

The Medical Staff
Fellowship Program

1990 Catalog

at the
National
Institutes
of Health



U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of
Health

22
107-15
1990

Please disregard all references to
the November 15, 1989 deadline for
receipt of applications.

NIH Medical Staff

Applications may be obtained from:

**The NIH Medical Staff Fellowship Program
Vicki Malick
Building 10, Room 1C125
National Institutes of Health
Bethesda, MD 20892
Tel: 301-496-2427**

**The National Institutes of Health does not discriminate
in employment on grounds of sex, race, color, age,
religion, handicap, or national origin.**

11/6/82

Says: Mrs. Lisa Hanover - x- 2427

1. only the deskset is available
- 2). Hard copy not yet purchased
- 3). The library is on their mailing list.

676

LIBRARY

FEB 23 1990

National Institutes of Health

The National Institutes of Health and the Warren Grant Magnuson Clinical Center, the research hospital for the Institutes, are international centers for biomedical research and clinical investigation. The Clinical Center and the other intramural research facilities in Bethesda have provided research and training opportunities for thousands of foreign scientists and physicians and for an even greater number of research scientists and clinical investigators in this country.

The Clinical Center has 500 beds to which patients are admitted for participation in research protocols. The protocols are directed towards understanding disease as well as towards diagnosis and treatment. The proximity of the wards to the 1,800 research laboratories ensures continuing collaboration between clinical and laboratory scientists. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Medical Staff Fellowship Program at the NIH.

John L. Decker, M.D.

Director



Contents

Part One

General Description of Medical Staff Fellowships and Other Opportunities

The Warren Grant Magnuson Clinical Center	1
The Medical Staff Fellowship Training Program	3
Dental Staff Fellows	4
Medical Staff Fellows in Pharmacology	5
Staff Physicians	5
Clinical Electives for Medical Students	5
Approved Training Programs	6
Endocrinology Fellowship Program	8
Medical Genetics Fellowship Program	10

Part Two

Applying for a Medical Staff Fellowship

Employment Benefits for Medical Staff Fellows	13
Method of Selection—Matching Program	13

Part Three

Institute Programs to Which Candidates May Apply

National Cancer Institute	15
National Eye Institute	59
National Heart, Lung, and Blood Institute	66
National Institute on Aging	83
National Institute on Alcohol Abuse and Alcoholism	94
National Institute of Allergy and Infectious Diseases	99
National Institute on Deafness and Other Communication Disorders	115
National Institute of Diabetes and Digestive and Kidney Diseases	116
National Institute of Child Health and Human Development	133
National Institute of Dental Research	157
National Institute of Arthritis and Musculoskeletal and Skin Diseases	166
National Institute of Environmental Health Sciences	169
National Institute of General Medical Sciences	177

National Institute of Mental Health	239
National Institute of Neurological Disorders and Stroke	266
The Clinical Center	
Transfusion Medicine	286
Clinical Pathology	286
Critical Care Medicine	290
Nuclear Medicine	292
Bioethics Program	292
Division of Computer Research and Technology	294

Part Four

Academic Programs Available to Medical Staff Fellows

Evening Courses	296
Combined Clinical Staff Conferences and Lectureships	296
The Washington-Baltimore Educational Complex	299
Library Facilities	299
Index	301

General Description of Medical Staff Fellowships and Other Opportunities

The Warren Grant Magnuson Clinical Center

John L. Decker, M.D.

Director

The Warren Grant Magnuson Clinical Center is a modern laboratory hospital facility shared by the 13 Institutes that conduct combined laboratory and clinical study programs. This 500-bed research hospital is located on a 300-acre campus at the National Institutes of Health (NIH) in Bethesda, Maryland.

NIH is the largest biomedical research organization in the world. Approximately 3,500 staff members have doctoral degrees, including almost 1,400 with M.D. degrees, more than 1,900 with Ph.D. degrees, and about 45 with D.D.S. and 80 with D.V.M. degrees. About 217 staff members have more than one doctorate.

Three Nobel laureates work on the campus: Drs. D. Carleton Gajdusek, Julius Axelrod, and Marshall W. Nirenberg. Dr. Gajdusek received the award in 1976 for his work in proving that kuru—a fatal disease affecting the nervous system—is a transmissible slow virus infection. In 1970, Dr. Axelrod was cited for discoveries concerning transmitter substances in nerve terminals and mechanisms for their storage, release, and deactivation. Dr. Nirenberg was honored in 1968 for his work on the translation of the genetic code and its function in protein synthesis.

Three other scientists received the Nobel prize for work done while at NIH. In 1976, Dr. Baruch Blumberg was honored for his discovery of the “Australia antigen,” a marker of hepatitis B. The prize was given to Dr. Christian Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA.

With the help of a staff of almost 3,000 technical personnel, NIH scientists are involved in some 2,500 research projects which result in more than 5,000 published scientific articles each year. The budget for this intramural research effort is approximately \$845 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physicians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care.

The Nuclear Medicine Department provides whole-body scanning and diagnostic imaging through the use of radioactive pharmaceuticals. Positron emission tomography and radionuclide cineangiography are among the imaging techniques under study. The superbly equipped clinical pathology laboratories provide optimum support to physicians and their patients. The Department of Transfusion Medicine provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for medical staff fellows to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of staff fellows in the use of computers in medicine.

A large, computer-based Medical Information System is used in support of patient care in the Clinical Center and the adjoining clinic. Two hundred display terminals and 85 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patient care process is available through the central NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 8,800 patients yearly. In addition, the outpatient clinics service over 145,000 patient visits annually.

A 13-story clinic, adjacent to the original Clinical Center structure, is designed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center. The facility provides an optimum environment to care for and study outpatients, yet retains the same proximity between clinical and laboratory scientists that has successfully promoted medical inquiry in the existing Clinical Center.

The Clinical Center appoints medical staff fellows for the Departments of Clinical Pathology, Critical Care Medicine, Nuclear Medicine, and Transfusion Medicine. These programs are described in Part Three.

The Medical Staff Fellowship Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as medical staff fellows at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Medical Staff Fellowship Program (formerly the Associate Training Program and encompassing what used to be designated clinical, research, and staff associate positions) are based on professional attainment, research interest, and ability. The NIH seeks outstanding candidates and selection is made without regard to race, sex, geographical location, or university affiliation. Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process explained in Part Two.

Each medical staff fellow participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each staff fellow's experience. Because of the unique blend of clinical and nonclinical scientists, the staff fellow is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorials to sponsored lectureships. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc.,

is available on a broad range of topics, including mathematics, languages, laboratory skills and clinical reviews (see Part Four).

The NIH affords the medical staff fellow the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

Some fellows devote most of their time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the staff fellow to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The medical staff fellow position also provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical categories. In these cases, the staff fellow may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he or she works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

The Dental Staff Fellow

Medical staff fellows in dentistry participate in directed laboratory and clinical research, under the guidance of NIDR senior investigators. In addition, fellows receive advanced clinical training in a program approved by the American Board of Oral Medicine. All fellows take postgraduate courses through the Foundation for Advanced Education in the Sciences, Inc. and participate in seminars, journal clubs and rounds to extend their clinical scientific background.

The Medical Staff Fellow in Pharmacology (Pharmacology Research Associate Program)

Staff fellows in this program, sponsored by the National Institute of General Medical Sciences, spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as medical staff fellows but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the Nation's medical and dental schools. For 1989-1990, the staffs of several Institutes are collaborating to supply an in-depth exposure to 16 clinical subspecialties: alcoholism, anesthesiology, clinical dental care (dental students), computers in clinical medicine, critical care medicine, endocrinology and metabolism, hematology-oncology, immunology, medical genetics, medical-surgical neurology, nuclear medicine, pain and neurobiology (medical and dental students), pediatric psychopharmacology, psychiatry/psychopharmacology, and surgical oncology. The essence of the educational experience is a close association between the student, medical staff fellows, and physician/scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged

to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Clinical Electives Program Office
Building 10, Room 1C125
National Institutes of Health
Bethesda, MD 20892

Approved Training Programs

Residency training programs approved by the Accrediting Council on Graduate Medical Education are offered in anatomical pathology, nuclear medicine, allergy and immunology, and transfusion medicine as are fellowships for advanced subspecialty training in transfusion medicine, and clinical pathology, including clinical chemistry, hematology, immunology, microbiology, and the laboratory computer service.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Anatomical Pathology

Lance A. Liotta, M.D., Ph.D.

Chief, Laboratory of Pathology

Building 10, Room 2A33
National Institutes of Health
Bethesda, MD 20892

Nuclear Medicine

Ronald Neumann, M.D.

Chief, Nuclear Medicine Department

Building 10, Room 1C401
National Institutes of Health
Bethesda, MD 20892

Allergy and Immunology

Michael M. Frank, M.D.

Clinical Director, National Institute of Allergy and Infectious Diseases

Building 10, Room 11N228

National Institutes of Health

Bethesda, MD 20892

Transfusion Medicine

Harvey G. Klein, M.D.

Chief, Department of Transfusion Medicine

Building 10, Room 5D56

National Institutes of Health

Bethesda, MD 20892

Board Certification: The first year of the clinical fellowship in the National Heart, Lung, and Blood Institute is accredited as a third year of training in internal medicine by the American Board of Internal Medicine.

The first year of the clinical fellowship in the National Institute of Mental Health is accredited as the final (PG-4) year of training in psychiatry.

The 3-year medical staff fellowship has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Credit towards board certification is offered in the following specialties and subspecialties:

Allergy

Clinical chemistry

Critical care medicine

Dermatology

Endocrinology

Hematology

Gastroenterology

Infectious diseases

Internal medicine (NHLBI only)

Medical genetics

Medical oncology

Microbiology

Neurology

Pediatric endocrinology

Pediatric genetics

Pediatric hematology/oncology
Pediatrics
Psychiatry
Reproductive endocrinology (obstetrics and gynecology)
Rheumatology
Transfusion medicine (blood banking and
immunohematology)

The amount of credit earned depends on the training completed and the acceptability of such to the individual board. Candidates are advised to consult the appropriate Institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During the clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 500-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Medical staff fellows selected by any of the three endocrinology branches of the National Institute of Diabetes and Digestive and Kidney Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) as well as the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Medical staff fellows from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Prospective applicants who would like further information on the program should write Bruce D. Weintraub, M.D., Building 10, Room 8D14, National Institutes of Health, Bethesda, MD 20892 or telephone (301) 496-3405.

Lectures and Courses

The NIH campus provides a stimulating intellectual environment for continuing education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. The endocrinology fellowship program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an extensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program

Students selected from various medical schools throughout the country participate in endocrinology courses offered three times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations

Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the fellowship program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Bruce D. Weintraub, M.D., Building 10, Room 8D14, National Institutes of Health, Bethesda, MD 20892 or telephone (301) 496-3405.

Medical Genetics Program

The NIH Interinstitute Medical Genetics Fellowship Program is a cooperative undertaking involving several clinical branches and research laboratories in various Institutes located on the Bethesda campus. It is a program of 2-years duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is also designed to fulfill all requirements of the American Board of Medical Genetics for fellowships leading to eligibility for Board certification. Fellows are expected to sit for Board examinations. The program has been accredited by the Board for all five medical genetics subspecialties.

The fellowship includes clinical activities and laboratory or clinical investigations under the direction of a senior scientist. Fellows are responsible for outpatients seen at the weekly NIH Genetics Clinic. They also serve as genetics consultants in the 500-bed Clinical Center and participate in weekly post-clinic patient conferences. Further opportunities to become familiar with the spectrum of patients with genetic disease are provided by attendance at genetics clinics at collaborating institutions including the Johns Hopkins Hospital, Children's Hospital National Medical Center Pediatrics Genetics Unit, George Washington University Wilson Unit (Prenatal Diagnosis) and the National Naval Medical Center.

Entrance into the Medical Genetics Program is through either of two routes: 1) individuals may apply to it directly, be interviewed by representatives of the Program's Steering Committee, and at the same time or after being accepted by the Program, choose a laboratory in which to do research; alternatively, 2) individuals may apply to a research branch or laboratory in one of the participating Institutes, be interviewed by the representatives of that Institute, and then, after being accepted by that Institute and arriving at NIH, apply for entrance into the Medical Genetics Program. (Each research unit may have clinical requirements in addition to those of the Medical Genetics Program.) Candidates choosing the second route will be interviewed after they have begun their NIH Fellowships by the Program's Steering Committee which will decide their acceptability.

Fellows in the Medical Genetics Program pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating

scientists are provided in a brochure which will be supplied to fellowship applicants. The aim of this program is to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in medical genetics.

The fellowship program includes a mandatory seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, a year-long didactic course in clinical aspects of genetics and a journal club. Other opportunities for continuing education (clinical and basic science conferences, tutorial seminars, and postgraduate courses) are plentiful on the NIH campus and are encouraged. The fellowship program also sponsors a yearly 8-week elective in medical genetics for senior students from medical schools around the country; fellows assist in didactic lecture-demonstrations on the approach to patients with genetic diseases and in supervision of students in patient-related activities. These and other teaching opportunities develop the fellows' skills as educators in preparation for future academic careers.

Applications for the fellowship program should be directed to the Medical Staff Fellowship Office (see p. 12). Further information may be obtained by telephone from Drs. John J. Mulvihill or Dilys M. Parry at (301) 496-4947.

Applying for a Medical Staff Fellowship

About 125 medical staff fellows are appointed annually to positions emphasizing clinical or basic research. Fellows are employed through the Public Health Service (PHS) in special Civil Service appointments.

Minimum eligibility requirements for most medical staff fellowships include completion of 2 years of graduate medical training before entrance on duty. Application should be made between 1 and 2 years before desired date of appointment.

To be considered for a medical staff fellowship, completed application forms must be received in the NIH Medical Staff Fellowship Office, Building 10, Room 1C125, National Institutes of Health, Bethesda, MD 20892, by November 10, 1989.

Participants in the National Health Service Corps Scholarship Program are not eligible for consideration until after they have served obligated pay-back years in NHSC-designated areas of medical need.

To be eligible for a PHS appointment as a medical staff fellow, a candidate must meet the following requirements:

- Be a U.S. citizen or a permanent U.S. resident.
- Must have and must maintain a current valid and unrestricted license to practice medicine in a State or Territory as a condition of employment (or obtain one within 12 months) in order to render patient care.
- Meet the medical fitness standards.
- Be a graduate of an accredited medical, osteopathic, or dental school.
- Satisfactorily complete an internship (PGI) approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of the medical school curriculum or incorporated as part of residency training.)
- Foreign medical graduates—foreign nationals or American citizens who have received their medical degree from a medical school outside the United States, Puerto Rico and Canada and that is listed in the World Health Organization's *World Directory of Medical Schools*—must be certified by the Educational Commission for Foreign Medical Graduates (ECFMG). ECFMG certification may presently be obtained by passing the ECFMG examination, Visa Qualifying

Examination (VQE) or the Federal Licensing Examination (FLEX). In July 1984, a new two day Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS) replaced the ECFMG and VQE examinations.

Medical Staff Fellows Applying to Only One NIH Laboratory or Branch

Candidates may apply directly to one laboratory or branch. However, this approach limits the number of opportunities that might be available at the NIH.

Alternative Fellowship Mechanisms for U.S. and Foreign M.D.s and Ph.D.s

The Medical Staff Fellow Program is commonly employed for physicians who will deliver primary patient care for a significant portion of their fellowship time. A variety of other fellowship mechanisms are available for U.S. and foreign physicians and Ph.D.s who wish to work exclusively in the laboratory. Candidates in this category should correspond directly with the NIH laboratories and branches of interest.

Employment Benefits for Medical Staff Fellows

Medical staff fellows are entitled to the following benefits which are comparable to those offered to Civil Service employees: partial subsidy for health insurance and group life insurance, retirement benefits, occupational medical emergency service at NIH, compensation for injury, 13 working days of annual leave per year and the same amount of sick leave, and training at Government expense. Moving expenses (travel and transportation of household goods) up to a maximum of \$2,500 will be provided to medical staff fellows entering on duty. No return expenses will be provided.

Method of Selection—Matching Program

Selections for medical staff fellow appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Checklist." After reading Part Three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested.

The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review by the Institutes of all applications, a limited number of candidates will be selected for personal interviews after which the candidate submits his or her confidential preference list. *Applicants should only list programs in which they have specific interest and would accept if chosen. Applicants who check many areas in virtually all Institutes may hurt their chances for obtaining an interview. In a highly competitive selection system, failure to accept a position after the "match" compromises another candidate's opportunities.*

The NIH Medical Staff Fellowship Office will set up the interview and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which medical staff fellows may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *Applicants should only list programs in which they have a specific interest and would accept if chosen.*

National Cancer Institute

Samuel Broder, M.D.
Director

—Alan S. Rabson, M.D., Director

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states.

The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief. Medical staff fellow positions are available in many of these areas and fellows work exclusively with the branch or laboratory in which they are accepted. All fellows have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Clinical positions are available for medical staff fellows in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Fellows participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Division of Cancer Biology and Diagnosis

Appointments in Clinical Research

Appointments in Laboratory Research

Nonclinical positions are available in the following laboratories: Biochemistry, Molecular Biology, Immunobiology, Cell Biology, Genetics, Mathematical Biology, Tumor Immunology and Biology, and Cellular Oncology.

In general, fellows are engaged in original research under guidance of individual investigators who act as preceptors for the fellows.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NCI programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see p. 177.

Clinical Research Branches

• Dermatology Branch—

Stephen I. Katz, M.D., Ph.D.

Senior Investigators

Thomas J. Lawley, M.D.

Gary L. Peck, M.D.

Jay H. Robbins, M.D.

John R. Stanley, M.D.

Peter M. Steinert, Ph.D.

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic, neoplastic, and inflammatory states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin, and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; immunologic determinants of the cutaneous inflammatory response; physiology of lymphoreticular cells and lymphokine formation; DNA damage and repair mechanisms in cultured cells; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; genodermatoses; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; clinical, chemical, and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of

therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

• **Experimental Immunology Immunology Branch—**

Alfred Singer, M.D.

Senior Investigators

Howard B. Dickler, M.D.

Ronald E. Gress, M.D.

Pierre A. Henkart, Ph.D.

Richard J. Hodes, M.D.

David M. Segal, Ph.D.

Susan O. Sharrow, B.S.

J. Stephen Shaw, M.D.

Gene M. Shearer, Ph.D.

Dinah S. Singer, Ph.D.

John R. Wunderlich, M.D.

The Experimental Immunology Branch consists of 11 independent laboratories. Researchers are studying: 1) the cell biology of immune responses; 2) structure, regulation and function of genes involved in the immune response; 3) transplantation biology; and 4) tumor immunology.

Scientific programs of the individual laboratories, collegial rapport, collaborative studies and the shared work-in-progress seminars all contribute to branch research. Each staff fellow joins a branch laboratory and becomes an integral member of the research group. The staff fellow works closely with the laboratory senior investigator.

A wide variety of research techniques are used, including isolation, identification, cloning, and functional characterization of cells involved with immune responses; tissue culture procedures; characterization of cell-surface receptors; protein biochemistry; nucleic acid sequencing and recombinant DNA technology; gene transfection; flow cytometry; the generation and use of monoclonal antibodies; bone marrow transplantation; production of transgenic mice; selective reconstitution of immune cell function in immunodeficient hosts; the use of organ cultures for studying cell differentiation; and the use of genetically deficient cells and animal models for studying immune responses.

Specific areas of emphasis include the following:

Cell Biology—Cellular interactions are critical to immune responses. Understanding these interactions is a major interest of the Branch, with emphasis on the roles of products of the major histocompatibility complex (MHC) genes and other genes that regulate immune responses, antigen-specific receptors and accessory molecules on cell surfaces, and signal pathways that lead to immune responses or tolerance to antigens. Both human and murine models are used.

T Lymphocytes—Bone marrow stem cells, under influence of the thymus, differentiate into mature T cells that can distinguish autologous and foreign cells. The role of the thymus in T cell development and establishment of immunologic tolerance is studied, and functional effects of perturbing development of murine T lymphocytes from bone marrow stem cells are evaluated. Recent technical advances in cell separation and identification, molecular biology and use of monoclonal antibodies have opened new approaches for exploring events that control differentiation of T lymphocytes. Focus in on: 1) identifying distinct lineages of T cells and their relationship to T cell development, and 2) identifying and characterizing cell-surface receptors and ligands that signal activation or differentiation. The relationship between T cell receptor function, rearrangement of coding genes, clonal frequency, and clonal deletion of self-reactive T cells is studied. Autocrine growth factors for subclasses of T cells have been identified, and their regulation is explored. Antigen-independent, cell-surface adhesion molecules can determine the functional outcome of cell-cell interactions involving T cells and other cells; adhesion molecules are evaluated and correlated with specific functions such as immunologic memory.

B Lymphocytes—Studies are directed to understanding the role of various B lymphocyte membrane receptors in regulation of the growth, differentiation, and function of these cells both in normal individuals and in certain diseases. Of particular interest are receptors for immunoglobulin (Fc Receptors), identification of previously undescribed receptors and the physical and functional interactions between receptors.

Antigen Processing Cells—The mechanisms of antigen processing and presentation to responding lymphocytes are evaluated, and procedures are developed for increasing the efficiency of these steps.

Cytotoxic Cells—The cellular and biochemical basis for cytotoxicity is evaluated, including identification of the cells, relevant cell-surface receptors, triggering mechanisms and the subcellular mechanisms that mediate cytotoxicity.

Gene Expression—The structure, organization and regulation of expression of the class I MHC multigene family are studied. Genes under investigation are involved in cellular immunity, such as encoding transplantation antigens, and encoding differentiation antigens. Current efforts include the identification and characterization of intracellular and extracellular factors which affect MHC gene expression. The molecular mechanisms regulating the expression of these genes are analyzed by a combination of structural and functional analyses. Studies rely on the combined application of techniques of molecular, cellular and developmental biology.

Transplantation Biology—Basic mechanisms of T cell activation, effector function, and repertoire selection as related to organ and bone marrow transplantation are studied. Techniques for the depletion of normal and neoplastic T cells from human marrow are applied clinically and in experimental systems. Mechanisms of marrow graft rejection, enhancement of engraftment, and methods for directed transfer of genes into hematopoietic cells are examined. The mechanisms of graft-versus-host reactions and factors that enhance or suppress them are studied.

Tumor Immunology—Studies are directed towards identifying the cellular basis for MHC-restricted and non-restricted anti-tumor activity and towards activating and refocusing the immune system against tumors by use of bifunctional antibodies.

Autoimmunity—Immune regulation in autoimmune diseases is studied by analysis of T-lymphocyte function in murine models with lupus-like characteristics and in peripheral blood from SLE patients.

Acquired Immunodeficiency Syndrome—Helper T cell dysfunction in early stages of AIDS is characterized, and alternative pathways for T-dependent immune responses are identified.

• **Immunology Branch—**

David H. Sachs, M.D.

Senior Investigators

Christian LeGuern, Ph.D.

Megan Sykes, M.D.

The Immunology Branch researches basic immunology with particular emphasis on the major histocompatibility complex (MHC) and its role in transplantation in animal models and in humans. The areas of study are: 1) immunogenetics of the murine MHC; 2) development of models for the induction of specific tolerance to MHC products; 3) genetics of the miniature swine MHC; 4) molecular biology of porcine class II genes; and 5) studies of bone marrow and organ transplantation in animal models and in humans.

Immunogenetics of the Murine MHC—The maintenance of pedigreed inbred and congenic resistant strains of mice and for the development of new recombinant H-2 haplotypes of value for structural and functional studies of genes within the MHC is under way. The production of monoclonal antibodies reactive with products of MHC genes is studied. New strains bearing recombinant MHC haplotypes (of which 22 have been derived from the breeding program of the Immunology Branch) are utilized for the production of new reagents and probes to study the fine structure of the MHC.

Development of Models for the Induction of Specific Tolerance to MHC Products—The induction of intentional mixed chimerism across MHC barriers is investigated. Methods used produce complete allogenic chimerism while avoiding GVHD. Use of this model in treatment of leukemia is under investigation. The use of monoclonal anti-T-cell subset antibodies as a substitute for irradiation is explored. The effect of selective thymic irradiation on production of long-term mixed chimerism and specific tolerance across an MHC barrier with a non-lethal preparative regimen also is explored.

Genetics of the Miniature Swine MHC—Partially inbred strains of miniature swine, NIH mini-pigs, have been developed as a large animal preclinical model for transplantation studies. Five new recombinant haplotypes have been identified within these herds, and three of these have been bred to homozygosity. By serologic, biochemical and genetic data all of these

recombinants appear to have split class I from class II loci. Using these new recombinant MHC haplotypes, the relative importance of class I versus class II antigens for allograft survival is examined. The mechanism by which class II antigen matching assumes overwhelming importance in determining the outcome of vascular allografts is under investigation.

Molecular Biology of Porcine Class II Genes—A molecular approach to the analysis of class II genes in renal allograft species is carried out. This approach involves RFLP analysis, construction and analysis of genomic and cDNA libraries, and isolation and sequence analysis of porcine class II genes. The isolated cDNA genes are incorporated into retroviral constructs with the intent to transfer these genes between allogeneic individuals via transduction of bone marrow stem cells. The effects of this genetic engineering on the response to transplants will be examined.

Studies of Bone Marrow Transplantation—Preclinical studies of bone marrow transplantation regimens are carried out in miniature swine. The use of autologous T-cell depleted bone marrow to prevent lethal GVHD is studied in this model. Investigators plan to use this model for leukemia therapy studies.

Metabolism Branch—

Thomas A. Waldmann, M.D.

Louis M. Staudt, M.D., Ph.D.

- Cellular Immunology Section—

R. Michael Blaese, M.D.

Andrew V. Muchmore, M.D.

- Endocrine Section—

James M. Phang, M.D.

S. Peter Nissley, M.D.

- Immunophysiology Section—

David L. Nelson, M.D.

- Molecular Immunogenetics and Vaccine Research Section—

Jay A. Berzofsky, M.D., Ph.D.

The Metabolism Branch is concerned with clinical and laboratory studies that focus on the immunologic, endocrinologic, and metabolic basis of disease occurring in patients with neoplasia.

Immunologic interests encompass a broad area of immunological investigations. These studies are directed toward defining the factors involved in the control of the human immune response.

Major efforts are directed toward studies of the arrangement and rearrangements of the immunoglobulin and T-cell antigen receptor genes. Special emphasis is given to molecular analysis of translocations of putative transforming genes to a locus associated with the rearranging antigen-specific genes in patients with lymphoid tumors. The branch studies these areas: 1) the characterization of transacting regulatory factors, especially the octamer binding protein that control lymphoid-specific gene transcription; 2) the genetic control of the immune response to natural antigens with special emphasis on the development of algorithms for predicting molecular structures identified by T-cells and the use of these algorithms to develop vaccines against AIDS and malaria; and 3) the identification of unique cell surface determinants, especially receptors for growth factors on subpopulations of lymphoid cells with different functional capabilities using antibodies developed with hybridoma technology. These studies are directed toward the characterization of the function and structure of the multi-chain receptor for interleukin-2 and the cloning of the genes for this inducible cell surface receptor. Other studies are directed toward the development of techniques and reagents for use in the eventual application of gene therapy to human disease. Other areas include: 1) the isolation of biological modifiers that regulate the human immune response; 2) the analysis of action of immunoregulatory cells including helper T-cells, suppressor T-cells and macrophages that regulate antibody responses; and 3) disorders of these immunoregulatory cell interactions in patients with immune dysfunction.

Endocrine interests emphasize the mechanisms of hormonal and metabolic regulation that relate to human disease and physiology. These studies focus on: the interaction between growth factors, especially insulin-like growth factors I and II, and their specific receptors; the post-receptor mechanisms which transduce events at the cell surface into regulatory signals controlling cellular metabolism and gene expression; and the identification and isolation of genes coding for membrane receptors and for enzymes mediating post-receptor events.

Another focus is on the regulatory role mediated by the transmembrane transfer of reducing-oxidizing potential. Specifically the regulatory role of the metabolite of proline, pyrroline-5-carboxylate on major metabolic pathways including the activation of the pentose-phosphate pathway, stimulation of PP-ribose-P synthesis and on the production of nucleotides is defined.

Basic Research Laboratories

Laboratory of Biochemistry—

Claude B. Klee, M.D

The emphasis of the work in the laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development and differentiation. The study of regulation encompasses regulation of gene expression, regulation of interaction of macromolecules and regulation of cells by hormones and ions. Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology and molecular genetics.

- **Biosynthesis Section—**

Edward L. Kuff, M.D., Ph.D.

Studies of the molecular structure, evolution and expression of a family of endogenous transposable retrovirus-like elements (retrotransposons) in the DNA of mouse and other species, and the effects of these elements on cell function are among the major concerns of this section. The interactions between cells involved in the immune response and the identification and isolation of participating cell types also are studied.

- **Cellular Regulation Section—**

O. Wesley McBride, M.D.

Chromosome- and DNA-mediated gene transfer into heterologous mammalian cells is used to map human genes and to isolate restricted regions of the human genome. Somatic cell hybrids are employed to map various human genes to specific chromosome segments. The inflammatory response in guinea pigs is studied as a model for the regulation of granulocyte maturation.

- Developmental Biochemistry and Genetics Section—
Michael Yarmolinsky, Ph.D.

Biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The regulation of DNA synthesis in the cell cycle and the partitioning of replicons to daughter cells is studied in *Escherichia coli*. The structure of *Drosophila* chromatin is studied, as a basis for analyzing the regulation of gene expression during the development of germ cells and embryos. Currently under study are various proteins that interact with chromatin to regulate gene expression.

- Protein Biochemistry Section—
Claude B. Klee, M.D.

Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+} , calmodulin, and cyclic nucleotides. Emphasis is on analyzing the details of the calcium-mediated interactions between purified proteins. The structure-function relations involved in the regulation of myosin activity is studied at the level of protein structure.

- Nucleic Acid Enzymology Section—
Samuel Wilson, M.D.

Studies pertain to a variety of nucleic acid structural and functional relationships in eukaryotic cells and viruses. The proteins and enzymes involved in DNA synthesis in mammals are investigated as well as the genes that encode these proteins. The organization and function of repetitive sequences in primate DNA is investigated.

- Biological Interactions Section—
Beverly Peterkofsky, Ph.D.

Conducts studies to determine the mechanisms that regulate the biosynthesis of extracellular matrix components during normal growth and development. The effects of neoplastic transformation on these processes also is studied.

- Biochemistry of Gene Expression Section—
Bruce Paterson, Ph.D.

A molecular genetics approach is taken to study the structure, organization, and regulation of particular eukaryotic genes. Systems under investigation include those genes

involved in muscle and nerve cell differentiation and the metallothionein genes which control heavy metal sensitivity in eukaryotic cells. Yeast genetics are used extensively to study the metallothioneins.

Laboratory of Cell Biology—

Lloyd W. Law, Ph.D.

- Office of the Chief

The laboratory conducts investigations to identify and characterize, and to isolate and purify, tumor specific antigens using model systems in experimental animals. These studies require the use of immunologic, biochemical, somatic cell hybridization, gene cloning and monoclonal antibody production techniques. Studies include immunologic responses to tumor specific antigens both solubilized and soluble, obtained from spontaneous, chemically and virally induced neoplasms. Studies also involve identification of the genetic elements involved in tumorigenesis and in the induction of tumor specific antigens and the relationship between tumor induction and tumor antigens, using transfection techniques.

- Chemistry Section—

Ettore Appella, M.D.

This section focuses on different aspects of chemical immunology. One aim is to define the molecular nature of the unique transplantation antigens found among different tumors. This study involves the biochemical purification of such antigens, their chemical structure and gene cloning, and their role in tumor rejection. A second aspect is an investigation of the role played by the Class I and Class II histocompatibility antigens, both in the recognition of different antigens and the control of malignancy. This is being approached by site-directed chemical mutagenesis of cloned histocompatibility genes and expression of the mutant gene in L-cells. A third investigation is a basic approach to the problem of growth control by different transforming proteins using chemical synthesis.

Laboratory of Immunobiology—

- Cellular Immunity Section—
Berton Zbar, M.D.

The section identifies consistent genetic changes in adult solid tumors; explores the diagnostic and prognostic significance of such changes; clones recessive oncogenes; and suppresses the malignant phenotype by replacement of genes lost during malignant transformation.

- Immunopathology Section—
Edward J. Leonard, M.D.

The main goal of this section is to understand the basis for leukocyte accumulation at sites of inflammation. Cell biology and biochemistry of chemotaxis are studied. Methods including protein purification and sequencing, flow cytometry, monoclonal antibody generation, chemotaxis assays and toxic metabolite measurement are used to identify chemotactic factors, enumerate cell surface receptors, and study chemotactic stimulus-response pathways. *In vitro*, animal and human experiments are performed.

Laboratory of Molecular Biology—

Ira Pastan, M.D.

- Molecular Biology Section—
Ira Pastan, M.D.

Recombinant DNA methods are used to create novel cytotoxic molecules that kill cells bearing different receptors. Chimeric genes are created by fusing cDNAs encoding specific growth factors or other targeting molecules (transforming growth factor α , interleukin 2, IL6, CD4) to a modified *Pseudomonas* exotoxin gene. The chimeric genes are expressed in *E. coli* where chimeric cytotoxic proteins are produced. Selective destruction of cells bearing EGF, IL2 or IL 6 receptors or cells infected by the AIDS virus by chimeric toxins may be useful in the treatment of cancer, AIDS or various immunological disorders. In addition, new types of immunotoxins are constructed using genetically modified *Pseudomonas* toxin. Studies are also carried out on the molecular basis of drug resistance in human cancer. New genes responsible for drug resistance are isolated and characterized. Cell-free transcription is used to study control of the EGF receptor gene and the human multidrug resistance gene.

- Biochemical Genetics Section—
Susan Gottesman, M.D.

The section studies the regulation of gene expression in *E. coli* and the bacteriophage lambda, including analyses of the control of transcription initiation, transcription termination, and the role of protein stability in regulating protein availability; DNA replication and recombination in prokaryotes with emphasis on site-specific recombination.

- Ultrastructural Cytochemistry Section—
Mark Willingham, M.D.

This section focuses on the study of basic cellular mechanisms of cell and organelle movement and function using morphologic techniques, especially electron and light microscopic immunocytochemistry, image intensification microscopy of living cells, and direct microinjection of single cells in tissue culture.

- Membrane Biochemistry Section—
Kenneth Yamada, M.D., Ph.D.

The functions of plasma membrane and extracellular glycoproteins, such as fibronectin are examined in cell adhesion, migration, and metastasis, by biochemical, immunological and cell biological approaches in conjunction with site-directed mutagenesis and synthetic peptide analyses of protein function.

- Developmental Genetics Section—
Sankar Adhya, Ph.D.

To elucidate the mechanisms of control of gene expression in prokaryotes, genetic and biochemical experiments are conducted to determine how various regulatory molecules function to modulate transcription and/or translation.

- Molecular Cell Genetics Section—
Michael Gottesman, M.D.

Molecular and somatic cell genetic approaches are used to analyze malignant transformation, growth control, and multi-drug resistance of human tumor cells. Techniques employed include mutant isolation, gene transfer, and molecular cloning.

- Molecular Genetics Section—
Bruce Howard, M.D.

Research focuses on molecular mechanisms regulating cell growth, with an emphasis on identification of anti-oncogenes.

i.e., genes that suppress either cellular transformation or immortalization. Experimental approaches include molecular cloning, gene transfer, analytical FACS, and site-specific mutagenesis.

Laboratory of Pathology—

Lance A. Liotta, M.D., Ph.D.

Elaine S. Jaffe, M.D.

- Surgical Pathology and Postmortem Section—
Surgical Pathology Service—
Maria Merino, M.D.
Autopsy Service & Pulmonary Pathology—
William D. Travis, M.D.
- Hematopathology Section—
Elaine S. Jaffe, M.D.
- Cytopathology Section—
Diane Solomon, M.D.
- Tumor Invasion and Metastases Section—
Lance A. Liotta, M.D., Ph.D.
- Biochemical Pathology Section—
David P. Roberts, Ph.D.
- Ultrastructural Pathology Section—
Maria Tsokos, M.D.
- Gene Regulation Section—
David L. Levens, M.D., Ph.D.

The Laboratory of Pathology of the National Cancer Institute offers a 3-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of lung pathology, pediatric pathology, cardiac pathology, hematopathology, and neuropathology can be arranged. The research activities of the staff are varied, and participation in clinical or basic research projects is an intrinsic part of the program during elective periods. Research interests of the laboratory include: tumor molecular biology, DNA binding proteins and gene regulation, oncogenes, cell motility, immunopathology, mechanisms of metastasis, and tumor biology.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of the biochemistry and molecular genetics of cancer invasion and metastases, cell surface biochemistry of lymphocytes, protease structure and function, oncogene growth regulation in neoplastic cells, gene rearrangements in lymphomas, ultra-structural studies of neoplastic cells, and receptor biology.

Laboratory of Mathematical Biology—

Jacob V. Maizel, Jr., Ph.D.

The activities of the Laboratory of Mathematical Biology fall into several broad areas: macromolecular structure and function, membrane structure and function, immunology, pharmacokinetics, and computational and modeling methodology. The work is both theoretical and experimental. Application of theoretical understanding to these biological systems, which serve as models for aspects of the cancer process, is accomplished through the use of advanced computing. Close collaboration provides valuable feedback and knowledge transfer between these two research domains. The laboratory also develops computer methodology that is utilized by researchers of the entire biomedical community.

- **Molecular Virology—**

Jacob V. Maizel, Jr., Ph.D.

Human viruses are studied with the goal of understanding the molecular mechanisms, replication, synthesis, assembly, and interaction of viral genome-encoded macromolecules with the architecture and functions of their host cells. It is our goal to understand virus-cell systems through computer analysis, experimental molecular biology, and genetic engineering. General principles are found that are applicable to other human cellular systems since viruses depend on the cells almost entirely for their major biochemical machinery. In the past, findings from viral systems have led to discoveries concerning assembly of cell architectural elements, splicing of pre-mRNAs, nuclear-cytoplasmic interactions, and the associations between viral and cellular proteins involved in cell transformation. As a long-term goal we aim to define these systems in terms of the sequences of their genomes and the computed properties of the molecules encoded by them.

- Membrane Structure and Function—
Robert P. Blumenthal, Ph.D.

Research is conducted on the mechanism of membrane fusion mediated by viral spike glycoproteins. The mode of action of the G protein of Vesicular Stomatitis Virus (VSV), the HN and F proteins of Sendai Virus, and the HA protein of influenza virus also is being studied. Specific topics include: studies of membrane fusion of intact enveloped virus with liposomes and cells; reconstitution of viral spike glycoproteins into lipid vesicles using detergent dialysis and measurement of membrane fusion activity of the reconstituted viral envelope; study of the role of viral receptors in mediating viral entry; studies of structure, conformation, and cooperativity of viral spike glycoproteins; studies of fusion mechanisms using cloned viral membrane sequences expressed in transfected cells. Fusion and conformation is monitored using a variety of biophysical techniques, mainly based on fluorescence spectroscopy.

- Molecular Structure and Properties
Robert L. Jernigan, Ph.D.

Biopolymers and their conformations and properties are investigated from a theoretical viewpoint. In the basic research, new methods are developed to treat problems of current interest in molecular biology. Applications, typically computer intensive, are to globular proteins, membrane proteins, structural proteins and DNA-protein binding, especially with the aim of understanding molecular function through structure.

- Theoretical Immunology—
John N. Weinstein, M.D., Ph.D.

Monoclonal antibodies and other "biologicals" are investigated by a combination of theoretical and experimental techniques. The central paradox of the field is that these agents often function very efficiently *in vitro* but only marginally *in vivo*. Our aim is to figure out how best to apply them clinically in the contexts of cancer and AIDS. The approach is eclectic, involving elements of immunology, pharmacology, biophysics, molecular biology, and molecular structure analysis.

- Image Processing—
Lewis E. Lipkin, Ph.D.

The Image Processing Section works in the areas of nucleic acid structure, 2-D gel protein analysis and computer controlled and/or aided microscopy. This work is facilitated by several dedicated large mini-computers and a dedicated mainframe.

- Membrane Biology Section—
Pedro Pinto da Silva, Ph.D.

Our work proceeds along two main areas:

I. Structure and dynamics of plasma and intracellular membranes: we develop and apply new combinations of freeze-fracture and immunogold labeling methods (“fracture-label,” “label-fracture” and “fracture-flip”) to study the topology, structure, surface nanoanatomy and topochemistry of biological membranes.

II. Membrane fusion; structure and biogenesis of intercellular junctions: we study the freeze-fracture morphology of cellular processes that involve membrane fusion (e.g., exocytosis). We investigate also the morphology of specialized intercellular contacts—tight and gap junctions—viewed as stabilized intermediates of fusion between components of adjacent plasma membranes in eukaryotic cells.

Laboratory of Genetics— Michael Potter, M.D.

The laboratory consists of independent investigators who study aspects of experimental cancer genetics. Research is conducted on mineral oil-induced plasma cell tumors in mice. Studies focus on mechanisms involved in this form of carcinogenesis, such as the role played by susceptibility and resistance genes, mutated or over-expressed oncogenes, growth factors, pristane oil metabolism, chronic granulomatous tissue, cellular and humoral immunological factors. Studies also concern the origins of other forms of B cell and myeloid tumors which arise intraperitoneally following injections of oil. The model tumor systems are based on retrovirus insertions in particular genes, on retroviral vectors that have been constructed to over-express various oncogenes, and the effects that intraperitoneal pristane contributes to the pathogenesis of these tumors.

Research also is under way on the following: the pathogenesis of erythroleukemia in mice; the interactions of protein antigens and their antibodies; the mechanism of heavy chain deletion in IgD expression, studies on the factors regulating oncogene transcription in various B-cell and myeloid neoplasms; and the effects of mutations in certain oncogenes on their expression and transformation potential, the use of embryonic stem cells and homologous recombination to study the biological effects following inactivation of specific genes, and the identification and characterization of genes and their products involved in the control and regulation of cell growth and differentiation.

Laboratory of Tumor Immunology and Biology—
Jeffery Schlom, Ph.D.

The laboratory conducts research to identify immunologic markers specific for, or associated with, various human neoplasms, with the ultimate aim of applying these toward the diagnosis, prognosis, and treatment of human cancer. Specifically, the laboratory is engaged in studies involving the generation and characterization of monoclonal antibodies to tumor associated determinants with particular emphasis on the study of human carcinomas. Studies ongoing involve the conjugation of monoclonal antibodies to isotopes for utilization in the diagnosis and therapy of tumor cells. Monoclonal antibodies active in antibody dependent cell mediated cytotoxicity are also being investigated. Genetically engineered monoclonals are being developed and modified for both diagnostic and therapeutic applications. Immunoassays are being developed that will aid in the characterization of human tumor cell populations, and in the diagnosis or prognosis of certain human cancers. The laboratory is also engaged in studies to investigate the association between specific murine and human genetic elements and tumorigenesis, employing techniques of gene cloning and molecular hybridization.

• **Experimental Oncology Section—**
Jeffrey Schlom, Ph.D.

Projects include research to generate and characterize monoclonal antibodies that are reactive with mammalian carcinoma cells with emphasis on human breast, colon, ovarian, and lung carcinomas; to use monoclonal antibodies to

identify and characterize specific proteins that are associated with the neoplastic state, with emphasis on human carcinoma systems; and to develop immunoassays that will aid in the characterization of human carcinoma cell populations and in the diagnosis or prognosis of human carcinomas. The use of monoclonal antibodies and the development of genetically engineered recombinant-chimeric immunoglobulins is investigated to aid in the detection or therapy of carcinoma lesions. Experiments are conducted to determine those factors which influence the antigenic modulation, antigenic phenotype, and the state of differentiation of human carcinoma cell populations. Studies are ongoing to identify the genes coding for the expression of specific tumor associated antigens.

- Oncogenetics Section—

Robert Callahan, Ph.D.

This section seeks to identify and molecularly clone tumor specific cellular and viral genetic elements from human carcinoma and other mammalian tumors. Research is being conducted to determine the organization of tumor specific genetic elements in cellular DNA, and the biological activity and role of tumor specific genes in normal and neoplastic tissue. The ultimate aim is to develop an understanding of the genetic changes which are relevant to the etiology of human neoplasia.

- Biochemistry of Oncogenes Section—

Robert Bassin, Ph.D.

Investigations of the mechanisms of cellular transformation mediated by RNA tumor viruses and by related cellular oncogenes are under way, emphasizing the nature and functions of specific cellular proteins which are involved in the transformation process. Studies are being conducted to identify genetic elements responsible for tumorigenesis and for immunologic markers specific for various human carcinomas. Studies are also being carried out to investigate the cellular control mechanisms which are active in preventing infection and disease by endogenous RNA tumor viruses.

- Cellular and Molecular Physiology Section—

Herbert L. Cooper, M.D.

This section plans and conducts research on the mechanisms by which oncogenes and other tumorigenic modalities

disrupt normal cellular biochemical pathways to produce neoplastic cell growth. Emphasis is on modifications in the expression of genes for normal cell proteins and the translation and post-translation modification of their encoded protein products. Studies in progress concern the role of deranged synthesis of specific cytoskeletal proteins in the mechanism of oncogene action and tumor production. Other studies investigate biochemical events related to the regulation of cell differentiation in normal and neoplastic cells, and the structure and function of tumor-associated glycoproteins.

- Cell Cycle Regulation Section—

William R. Kidwell, Ph.D.

The program of this section focuses on the role of growth factor production by human mammary tumor cells in tumor initiation, growth and progression. Four growth factors have been purified from breast tumors. One of these acts on breast cells to promote synthesis of the basement membrane, a natural barrier against tumor invasion. This factor is high in well differentiated tumors and absent from metastatic tumors that do not make a basement membrane. Three other growth factors detected act synergistically to promote anchorage-independent growth, a characteristic of transformed cells. Studies are designed to characterize the receptors for these factors on tumor cells, to elucidate the mechanisms regulating expression of growth factors by different tumor types, and to determine whether the levels of the growth factors in tumors can be exploited for diagnostic, prognostic or therapeutic purposes for the treatment of breast cancer. Laboratory techniques include methods for breast cell culture, protein purification and characterization, immunological and biochemical analyses, and gene cloning.

- Cellular Biochemistry Section—

Yoon S. Cho-Chung, M.D., Ph.D.

This section studies the cellular mechanisms regulating the growth and regression of neoplasms. Emphasis is placed on the roles of cyclic nucleotides, hormones and other intracellular mediators in the growth control of normal and neoplastic cells. Current studies involve the roles of cyclic AMP and estrogen in the regulation of the expression of cellular proto-oncogenes, especially the *c-ras* gene in the established

mammary carcinomas as well as during mammary carcinogenesis. The ultimate aim of these studies is to apply these toward the diagnosis, treatment and prevention of human cancer.

Laboratory of Cellular Oncology—

Douglas R. Lowy, M.D.

Senior Investigators

- Kenneth S. S. Chang, M.D.

The Laboratory of Cellular Oncology actively supports training physicians and other scientists in experimental approaches of tumor and molecular biology. Initial staff fellowship appointments are for two years, with the possibility of renewal.

Specific research projects are developed jointly by the staff fellow and the supervisor. These choices are based on the long-term objectives of the fellow and the research interests and expertise of the laboratory. Fellows participate fully in the laboratory's regular meetings that discuss current journal articles, analyze data obtained by investigators in the laboratory and speakers from outside the laboratory. For Dermatologists in training, a combined clinical and research program (with up to one year of Residency credit towards Board eligibility) is available in conjunction with the Dermatology Branch, NCI.

The laboratory carries out research on the genetics and immunology of oncogenesis. The studies seek to identify critical differences between normal and neoplastic cells. The purpose of these investigations is to acquire information on gene expression and protein function that may ultimately lead to improved diagnosis, therapy, or prophylaxis of neoplastic diseases.

Investigators in the laboratory probe the mechanisms by which normal cells become neoplastic through studying the effects of viral and cellular transforming genes (oncogenes) on tissue culture cells or experimental animals. Alteration of tumor growth patterns by the immune system and by biological modifiers such as interferon is also studied. Tumor virus systems utilized in the laboratory include polyomaviruses and papilloma-viruses, rodent and primate retroviruses, and acute transforming retroviruses. The biology of papilloma-viruses and of the *ras* oncogenes have been the focus of many studies in the laboratory.

A wide range of experimental techniques are employed in carrying out these studies. These include gene cloning by recombinant DNA technology, DNA mediated gene transfer, morphological transformation of tissue culture cells, quantitative virological assays, fractionation of sub-cellular components, radioimmunoassays, molecular hybridization, DNA binding assays, and *in vitro* mutagenesis.

Division of Cancer Etiology, NCI

—Richard H. Adamson, Ph.D., Director

The Division of Cancer Etiology plans and directs laboratory, field and epidemiologic and biometric research on the cause and history of cancer. It studies prevention of cancer through direct intramural research, research grants and contracts; evaluates mechanisms of cancer induction and promotion by chemicals, viruses and environmental agents; serves as the focal point for the federal government on the synthesis of clinical, epidemiological, and experimental data relating to cancer causation; and advises the Institute Director on basic research activities as they relate to cancer cause and prevention. The intramural program conducts a basic laboratory research program on the causes of cancer by chemical, physical, and biological (viral) factors; and on the pathogenesis and prevention of various cancers.

Laboratory of Biology—

Joseph A. DiPaolo, Ph.D.

The Laboratory of Biology pursues a basic laboratory research program investigating the modulation of the transformation process that leads to malignancy. The primary objective is to determine the crucial molecular and physiological changes that occur in mammalian cells which have been exposed to chemical or physical agents or transfected with DNA as they undergo transformation from the normal growth controlled to the neoplastic state. The present emphasis in both animal and human cell models of carcinogenesis is the study of oncogenes and DNA changes which are responsible for the activation of genes in neoplasia. Currently there is an emphasis on papillomaviruses associated with sexually transmitted diseases. Human papilloma DNA, for example, is being used to transform several types of human epithelial cells; alterations in cell replication, gene expression, chromosomal structure, and

response to external growth regulatory signals are being analyzed in relation to stages in the transition to neoplasia. The research program within the Laboratory is a comprehensive and integrated approach to identifying both the genetic factors within the target cell as well as the physiological components provided by the host environment that are critical in inducing and modulating carcinogenesis. The role of growth factors, in particular leukoregulin, is being investigated to elucidate one form of intervention by which the host is able to modulate and even prevent carcinogenesis. Leukoregulin is a lymphokine or immunologic hormone which is noncytotoxic to normal cells and is capable of inhibiting the transformation process. A wide variety of molecular, biological, and histotechnological approaches are utilized in identifying both the factors that induce the changes leading to neoplastic transformation as well as those present intracellularly or extracellularly that assist in maintaining normal growth control and that make cells refractory or less susceptible to neoplastic conversion.

Laboratory of Experimental Carcinogenesis—

Snorri S. Thorgeirsson, M.D., Ph.D.

The Laboratory of Experimental Carcinogenesis plans, develops, and implements a research program to elucidate mechanism(s) of malignant transformation in human and animal cells by chemical carcinogens and other cancer causing agents; to determine critical cellular and genetic factors involved in initiation, promotion and progression of these transformed cells, and to apply, whenever possible, the knowledge obtained from these studies towards effective prevention of cancer in humans. Studies are designed to 1) identify and characterize exogenous and endogenous factors controlling initiation, promotion and progression of chemically induced tumors; 2) elucidate the regulation of gene expression and differentiation in both human and animal neoplasia; 3) define the mechanism by which modifiers of cellular differentiation may inhibit and/or promote the neoplastic process; and 4) characterize the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines. The laboratory is composed of three sections, each responsible for portions of the laboratory goals. The sections interact in an integrated approach to understand the mechanisms of carcinogenesis.

- Chemical Carcinogenesis Section—
Snorri S. Thorgeirsson, M.D., Ph.D.

This section plans and develops laboratory research aimed at elucidating the mechanism(s) of malignant transformation in human and animal cells by chemical carcinogens and other cancer causing agents. The major effort of the Section is focused on : 1) identification and characterization of exogenous and endogenous factors controlling initiation, promotion and progression during chemical hepatocarcinogenesis and in human mammary tumors; 2) applying advanced quantitative two-dimensional gel electrophoresis techniques of total cellular proteins to study protein changes during oncogenesis and to identify gene product(s) that are associated with the malignant transformation; 3) studies on the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines, and 4) definition of the mechanism by which exogenous agents and neoplastic development modify the expression and function of the multidrug resistance gene family.

- Hormone Action and Oncogenesis Section—
Gordon L. Hager, Ph.D.

This section plans and develops laboratory research on the mechanisms of the regulation of gene expression by hormones and growth factors. The major effort of the section is focused on: 1) characterization of the regulation of mouse mammary tumor virus expression by glucocorticoid hormones using advanced recombinant DNA techniques; 2) developing methods for *in vitro* DNA mediated gene transfer; and 3) studies of the mechanism on the action of growth factors and other transformation related with particular emphasis on characterization of the cellular receptors.

Laboratory of Comparative Carcinogenesis— Jerry M. Rice, Ph.D.

The Laboratory of Comparative Carcinogenesis plans, develops, and conducts a research program on effects of chemical carcinogens in rodents and in nonhuman primates in order to identify differences between species that are of importance for interspecies extrapolations of the effects of chemical agents, including extrapolations to humans. The research of the laboratory is oriented toward identification, description, and

investigation of mechanisms for interspecies differences and for cell and organ specificity in chemical carcinogenesis.

The laboratory consists of four sections: Tumor Pathology and Pathogenesis Section, Chemistry Section, Inorganic Carcinogenesis Section, and Perinatal Carcinogenesis Section. In addition, there is a research working group on nonhuman primates. Major areas of research within the laboratory include studies on transplacental chemical carcinogenesis in rodents and in nonhuman primates; the relation of morphogenetic differentiation to prenatal susceptibility to carcinogens; activation of cellular oncogenes during chemical carcinogenesis; identification of tumor promoters through *in vivo* experimentation; mechanisms underlying cellular specificity, as well as dose/effect relationships, for tumor promotion in internal organs in different species including nonhuman primates; investigation of carcinogenesis by toxic metals; characterization and histogenetic studies of experimental tumors by immunohistochemistry and histochemistry, and by light and electron microscopy; and mechanisms underlying the organ-specific carcinogenic properties of major classes of chemical carcinogens including N-nitroso compounds.

Laboratory of Cellular and Molecular Biology—

Stuart A. Aaronson, M.D.

The Laboratory of Cellular and Molecular Biology directs a comprehensive research program to 1) identify, isolate and characterize the transforming genes of acute transforming retroviruses; 2) elucidate the molecular mechanisms of transformation by retroviruses and retroviral *onc* genes; 3) determine the role of cellular DNA analogues of retroviral transforming genes in naturally occurring malignancies of human and other species; 4) identify, isolate and characterize transforming genes of human tumor cells; 5) elucidate the mechanisms by which replication-competent type C viruses cause leukemia; 6) search for new mammalian retroviruses and establish their origins and evolutionary relationships to known oncoviruses; 7) apply techniques developed in the investigation of naturally occurring and virus-induced cancers of animals to the search for viral etiology of human tumors; and 8) analyzes the effect of environmental agents or specific mechanisms which control and promote transformation in mammalian cells.

Laboratory of Cellular Carcinogenesis and Tumor Promotion—

Stuart Yuspa, M.D.

The Laboratory of Cellular Carcinogenesis and Tumor Promotion plans, develops and implements a comprehensive research program to determine the molecular and biological changes which occur at the cellular and tissue levels during the process of carcinogenesis. Studies are designed to define normal regulatory mechanisms for cellular growth and differentiation; determine the mechanism by which carcinogens alter normal regulation and the biological nature of these alterations; investigate the mechanism by which tumor promoters enhance the expression of carcinogen-induced alterations; identify cellular determinants for enhanced susceptibility or resistance to carcinogens and tumor promoters; and elucidate the mechanism by which certain pharmacologic agents inhibit carcinogenesis.

The laboratory is composed of three sections, each charged with a major responsibility for portions of the laboratory goals. Because of the integrated approach toward an understanding of mechanisms of carcinogenesis, considerable interaction occurs among the sections.

- **The *In Vitro* Pathogenesis Section—**

Stuart Yuspa, M.D.

This section develops relevant model systems for the study of all phases of the process of carcinogenesis; defines regulatory mechanisms for the normal control of growth and differentiation and alterations in these controls induced by initiators and promoters; clones and characterizes genes involved in differentiation of normal and tumor cells; studies functional alterations in gene expression produced by initiators and promoters and the mechanism by which these functional changes occur; and elucidates factors which determine susceptibility to carcinogenesis.

- **The Differentiation Control Section—**

Luigi DeLuca, Ph.D.

This section studies the biological and biochemical factors involved in normal differentiation of epithelial tissues; uses pharmacological techniques to alter differentiation of normal, preneoplastic and neoplastic epithelial cells to determine the relevance of differentiation to carcinogenesis and to determine

methods to intervene in preneoplastic progression; studies the relationship between differentiation and growth control; and focuses on cell surface changes in differentiation and neoplasia.

- The Molecular Mechanisms of Tumor Promotion Section—Peter Blumberg, Ph.D.

This section studies the interaction of promoters with specific cellular receptors; elucidates the functional importance of receptors in promoter action; identifies endogenous ligands with specific affinity for receptors of exogenous promoters; and characterizes the initial biochemical steps in the cascades associated with receptor occupancy. Particular attention is focused on the major target of phorbol ester action, protein Kinase C. In approaching these goals, the laboratory utilizes the latest technology in cell and molecular biology, as well as biochemical, pharmacological and immunological methods.

Laboratory of Experimental Pathology— Umberto Saffiotti, M.D.

This laboratory develops research on the experimental pathology of carcinogenesis, especially concerned with the induction of neoplasia by chemical and physical factors in epithelial tissues. It focuses on the development, characterization, and evaluation of experimental pathology models of epithelial cancer, *in vivo* and *in vitro*. Present emphasis is on respiratory carcinogenesis models, epithelial-mesenchymal relations in the pathogenesis of lung cancer and host factors in carcinogenesis by silica and other particulates.

Chemically defined, serum-free culture methods are developed to identify optimal conditions for growth, differentiation, and neoplastic transformation of epithelial cell systems. Mechanisms involved in the control of cell differentiation, transformation, and gene activation are studied.

Chemical carcinogenesis mechanisms are investigated in various cellular model systems for different end-points, such as cytotoxicity, DNA damage, mutation, transformation, and induction of metastatic activity.

Laboratory of Human Carcinogenesis—

Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess a) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, b) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation; and c) host factors that determine differences in carcinogenic susceptibility among individuals.

Molecular Genetics and Carcinogenesis—Investigation of the mechanisms of neoplastic transformation of human epithelial cells; activation of proto-oncogenes by chemical and physical carcinogens; inactivation and dysregulation of tumor suppressor genes by chemical and physical carcinogens; and direct and indirect mechanisms of genotoxicity caused by chemical and physical carcinogens.

In Vitro Carcinogenesis—Studies of phenotypic and genetic alterations during *in vitro* carcinogenesis; assessment of the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and identification of extra-, inter-, and intra-cellular factors modulating growth and differentiation of human epithelial cells.

Molecular and Biochemical Epidemiology—Measurement of gene polymorphism by molecular approaches, e.g., DNA restriction fragment length polymorphism, to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens.

Laboratory of Molecular Oncology—

Takis S. Papas, Ph.D.

This laboratory plans and conducts research on the molecular elements responsible for the development and expression of malignant phenotypes in humans and animals; and applies skills in molecular biology, recombinant DNA technology and hybridoma-monoclonal antibody production in a comprehensive program to identify and isolate cellular transforming genes and to characterize products expressed by these genes.

- Microbiology Section—

Donald G. Blair, Ph.D.

This section is concerned with the biological analysis of oncogenes in human and non-human genomes, and in the development of biological assays using animal models and tissue culture techniques to detect and isolate such genes and to determine the factors necessary for them to cause neoplastic transformation and tumor growth.

- Carcinogenesis Regulation Section—

Takis S. Papas, Ph.D.

This section studies the relationship between oncogenic viral gene expression and the conversion of cells from normal to transformed phenotype; and tests specific regions of molecular cloned acute transforming activity and elucidates the molecular mechanisms of interaction with the cell.

- Transgenic Analysis Section—

Takis S. Papas, Ph.D. (Acting)

This section 1) designs and carries out an integrated research program to characterize and identify the regulatory and molecular elements involved in expression and function of genes controlling critical cellular processes; 2) develops new assays to test the function of genes introduced into living tissue and cells employing a variety of methods, including microinjection, electroporation and calcium phosphate mediated gene transfection procedures; and 3) evaluates genes introduced into intact animals and tissue for phenotypic and genotypic expression by a variety of molecular and cell biological techniques employing recombinant DNA methodology.

Laboratory of Molecular Virology—

Edward Tabor, M.D. (Acting)

This laboratory is interested in the normal and abnormal regulation of gene expression. Methods from molecular biology, virology and cell biology are used to determine what signals regulate gene expression. The laboratory is interested in both viral (SV40, JCV, HTLV-I, HIV) and eukaryotic genetic units. The research efforts are focused on genes that are regulated at the level of transcription and that, in some cases, are responsive to induction by growth factors or trans-acting proteins.

The laboratory has made a commitment to the study of oncogenes and their role in transformation. Studies include mechanisms by which proto-oncogenes and their oncogenes function, particularly the *ras* genes of yeast *Saccharomyces cerevisiae*. HIV virus gene expression and gene manipulation in yeast are used to study HIV gene products.

Laboratory of Tumor Virus Biology—

Peter M. Howley, M.D.

This laboratory has a training program for M.D.s. and Ph.D.s. in molecular biology and viral oncology. Specific research projects are carried out under the direction of one of the four senior investigators in the laboratory.

The laboratory engages in several areas of research to determine critical cellular and molecular factors involved in virus-associated transformation and carcinogenesis. Studies are designed to identify and characterize exogenous viruses associated with the initiation or progression of neoplasia in humans or in animals as models for human neoplasia. Tumor virus systems studied in the laboratory include the polyomaviruses and the papillomaviruses. A major research effort of the laboratory is focused on the molecular biology of the papillomaviruses. Specific projects are designed to elucidate the factors involved in transcriptional regulation, transformation, plasmid replication, and immortalization functions encoded by these viruses. Investigators in the laboratory also study the molecular and biochemical mechanisms of oncogenic transformation by the polyomaviruses and the interactions of their encoded transforming proteins with cellular regulatory proteins. One group of cellular proteins being studied by the laboratory are the cellular tyrosine kinases, including *src* and *lck*. The laboratory has also been involved in the development of the papillomaviruses as mammalian cell cloning vectors and is interested in using these vectors to study the regulation of gene expression.

Laboratory of Viral Carcinogenesis—

Stephen O'Brien, Ph.D.

This laboratory is committed to basic research approaches to unravelling the genetic and cellular mechanism of neoplastic transformation in man and in mammalian model systems. Studies are conducted on the specific cellular genes which

participate in transformation from several distinct approaches. Endogenous mammalian retroviruses are studied in attempts to understand their role in gene regulation and in neoplasia. Transforming viruses, their included oncogenes and their ancestral cellular homologues are being examined using recombinant DNA technologies and systems for studying their expression during development and during carcinogenesis. Molecular processes of chemical carcinogenesis are studied using gene cloning, cell transfection and cell biology procedures. Somatic cell genetic approaches to neoplastic transformation is an important component of the laboratory as are the cytogenetic consequences of transformation. A new program of human genetics is under development in the laboratory using DNA polymorphisms to identify human genes which confer sensitivity or resistance to human viruses including HIV and Hepatitis B. In addition, the laboratory is also studying the genetic structure of human and animal populations with specific emphasis on genetic influences on viral epidemiology.

Laboratory of Tumor Cell Biology—

Robert C. Gallo, M.D.

The objectives of the Laboratory of Tumor Cell Biology are to develop, implement, and analyze data obtained from studies of cellular proliferation, cell differentiation, and biochemical growth characteristics of normal and malignant mammalian cells both *in vivo* and *in vitro*. Particular attention is given to hematopoietic cells, their normal behavior and especially changes seen during leukemogenesis. The laboratory focus is on the studies on human leukemias, lymphomas, acquired immune deficiency syndrome (AIDS), and AIDS-related complex (ARC). It is anticipated that an enhanced understanding of cell regulatory mechanisms will permit the optimal use of anti-tumor agents in the therapy of cancer, AIDS and the development of new approaches. Many studies are directed to the origin of these diseases, especially the role of certain viruses and certain cell genes called “*onc*” genes.

The Laboratory of Tumor Cell Biology is concerned with several biological and biochemical problems: 1) Studies on the cellular and molecular origin and pathogenesis of human leukemia and AIDS. Biochemical control mechanisms involved in

cell differentiation and neoplastic transformation are examined. Tumor viruses of animals are used both as tools (to define and isolate genes and gene products important for growth in man) as well as for help in understanding mechanisms of naturally occurring animal leukemias. Also, studies designed to determine the involvement of human lymphotropic retroviruses (HTLV) in T-cell malignancies and AIDS are intensively investigated. 2) Studies on the biochemical events preceding mitosis appear essential to the control of proliferation. Information derived from such studies may lead to a better understanding of the control of cell proliferation and development of more effective inhibitors of neoplastic cell growth. 3) Attempts to develop new approaches to cancer chemotherapy and to control AIDS using information gained from basic cellular studies. 4) Studies on the development of biochemical and immunological markers for malignant cells. Biochemical and immunological studies are also conducted in individuals with disorders associated with an increased incidence of neoplasia and AIDS or AIDS-related complex (ARC). 5) Controls regulating cellular growth and differentiation, and the process of malignant transformation in hematopoietic cells. 6) Growth factors (and their receptors) that control the growth and differentiation of blood cells have been isolated and are under intensive study, e.g., T-cell growth factor (TCGF), CSF, and related hematopoietic growth effecting molecules. 7) Human T-lymphotropic virus ((HTLV) has been isolated from patients with T-cell malignancies and AIDS and AIDS-related complex (ARC). Biochemical, biological and molecular biological studies to characterize HTLV belonging to different subgroups (I, II, III, IV), and seroepidemiological studies to determine the extent of HTLV infection in patients with T-cell malignancies; AIDS and AIDS-related complex (ARC) around the world are in progress. Attempts to obtain antiviral agents that block virus replication and develop a vaccine especially against the AIDS virus are also in progress. 8) A human DNA virus, belonging to the herpes virus family, has been isolated from lymphocytes of patients with either lymphoma or other immune disorders. The new DNA virus can infect, and eventually kill, B-cells in culture and is called human B-cell lymphotropic virus (HBLV). Biochemical, biological and molecular biological studies, to characterize the virus and

seroepidemiological studies to determine the extent of infection with this virus in different malignancies, are pursued.

Epidemiology and Biostatistics Program—

Joseph F. Fraumeni, Jr., M.D.

Associate Director

Medical staff fellow positions are available for 2-year assignments in four branches of the Epidemiology and Biostatistics Program, which provides a focus for epidemiologic and biostatistical research within the Institute. The program conducts epidemiologic investigations into the environmental and host determinants of human cancer; analyzes the natural history of cancer and the efficacy of therapeutic and preventive measures; and designs statistical models for clinical and experimental investigations.

Environmental Epidemiology Branch—

Robert N. Hoover, M.D.

The Environmental Epidemiology Branch conducts a wide range of studies to clarify the risk of cancer among persons exposed to occupational, nutritional, medicinal, radiogenic, infectious or other environmental hazards, and among persons with genetic or immunologic predisposition. Multidisciplinary studies with laboratory scientists are carried out whenever feasible.

Clinical Epidemiology Branch—

Robert W. Miller, M.D.

The Clinical Epidemiology Branch investigates the origins of human cancer by starting from peculiarities of cancer occurrence recognized at the bedside and studied through the disciplines of clinical medicine, epidemiology, and cellular genetics and other laboratory sciences. Current emphasis is given to the clinical delineation of cancer family syndromes and disorders that predispose to cancer, such as neurofibromatosis and certain birth defects, and to studies evaluating the late effects of cancer treatments, including reproductive toxicity. Liaison is maintained with many clinical services throughout the Washington area and beyond, as well as with the NIH Interinstitute Medical Genetics Program. Physicians selecting this branch need not have specific training in epidemiology or

genetics, and may become Board-eligible in medical genetics through the NIH Interinstitute Medical Genetics Program.

Radiation Epidemiology Branch—

John D. Boice, Jr., Sc.D.

This branch conducts studies to identify and quantify the risk of cancer in populations exposed to ionizing radiation, especially at low-dose levels. These include patient populations given diagnostic or therapeutic radiation alone or in combination with cytotoxic drugs and other forms of treatment.

Biostatistics Branch—

William J. Blot, Ph.D.

The Biostatistics Branch uses biometric and mathematical approaches to investigate the distribution, causes and natural history of cancer. New statistical methods are developed for designing and analyzing epidemiologic, clinical, and experimental studies of cancer. Mathematical models are explored to clarify processes of cancer biology and carcinogenesis, and improve methods of quantitative cancer risk assessment.

Division of Cancer Treatment

—Bruce A. Chabner, M.D., Director

This Division carries out a broad program of basic and clinical research concerning the treatment of cancer. The major areas of research are radiation therapy, drug therapy, modifiers of tumor growth and differentiation, and surgical approaches to cancer treatment. Treatment programs are multidisciplinary in nature, involving the cooperative efforts of medical, surgical, and radiotherapy staff members.

Cancer Therapy Evaluation Program—

Michael A. Friedman, M.D.

Associate Director

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials with investigational chemotherapeutic agents. This includes the incorporation of effective chemotherapeutic combinations in early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities until now considered

untreatable. For these purposes, the program has planned and helped organize several study groups designed to test combined modality approaches to specific diseases. The program also supports, through the cooperative agreement mechanism, various clinical cooperative groups made up of university hospitals, cancer centers, and community hospitals. These cooperative groups share in design, development, execution, and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research efforts at a national level. Staff members of the program attend meetings of the clinical cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between in-house preclinical and clinical programs and extramural activities.

Clinical Investigations Branch—

Richard S. Ungerleider, M.D., Chief

The Clinical Investigations Branch monitors and coordinates a broad range of research activities. This includes research support for individual investigator-initiated projects (R01), program project grants (P01), cooperative group agreements (U10), and planning grants (P20). This research spans the spectrum from laboratory research to Phase III clinical trials. Staff responsibilities include critical review and participation in the development of protocols developed by cooperative groups and intergroup studies. Staff members also develop overviews of research progress, formulate strategies for future research directions, and plan discussion groups on selected topics. There is a major emphasis on integration of modalities in the treatment of cancer.

This branch also maintains liaison with international clinical research groups.

Investigational Drug Branch—

Michael J. Hawkins, M.D., Chief

The Investigational Drug Branch (IDB) is responsible for the early clinical development of new biological and cytotoxic agents with potential antitumor activity. Physicians are assigned drugs based on the agent's putative mechanism of action. After

evaluation of the preclinical data, the drug monitor draws up a plan for the agent's development. Each protocol must be reviewed and approved by the drug monitor before the study may be initiated. Phase I studies are usually conducted by institutions under contract to the NCI and data is reported to the IDB for review by the drug monitor on a monthly basis. Extensive interactions with extramural investigators and the pharmaceutical industry are required.

Clinical Oncology Program—

Samuel Broder, M.D.

Associate Director

The Clinical Oncology Program (COP) recruits approximately 18 medical staff fellows each year for a 3-year assignment in medical oncology or a 2-year assignment in surgical oncology. Fellows are recruited for one of the following clinical branches: Medicine, Pediatrics, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-Navy Medical Oncology Branch located at the Naval Hospital Bethesda (NHBETH), Bethesda, Maryland. The program also offers a residency training program in radiotherapy.

The 3-year medical oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine or pediatrics. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients. The staff fellow may sometimes take a full year with a single clinical service, or take two 6-month rotations through the clinical services of the COP. The second and third years consist of clinical and/or laboratory research under the supervision of a member of the senior staff. Medical staff fellows will have the opportunity to select a project from the numerous current studies in the laboratories of the Clinical Oncology Program, the Developmental Therapeutics Program, or the Biological Response Modifiers Program. Opportunities are also available for clinical trial monitoring in the Cancer Therapy Evaluation Program. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second- and third-year medical staff fellows continue to follow patients in the Outpatient Department. Offered throughout the program are lectures, clinical conferences,

research seminars, teaching rounds, and joint conferences relevant to the field of clinical oncology and cancer research. Certain clinical conferences are mandatory.

Candidates otherwise qualified who successfully complete the program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology.

For further information, applicants to the medical or pediatric oncology training programs should write to Associate Director, Clinical Oncology Program, National Cancer Institute, Building 10, Room 12N214, Bethesda, MD 20892.

The Surgery Branch offers a 2-year surgical oncology training program. This program consists of a 6-month period on the wards of the Surgery Branch, inpatient and outpatient services, and 1½ years in one of the laboratories of the senior staff in the Surgery Branch. Selected medical staff fellows may remain for a third year to continue their laboratory research. Applicants interested in the Surgery Branch program should write director Steven Rosenberg, M.D., Ph.D., Surgery Branch, Building 10, Room 2B42, National Cancer Institute, Bethesda, MD 20892.

Applicants interested in the radiotherapy residency should write to Eli Glatstein, M.D., Radiation Oncology Branch, Building 10, Room B3B69, National Cancer Institute, Bethesda, MD 20892.

Medicine Branch—

Charles E. Myers, M.D.

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, prostate cancer, breast cancer, ovarian carcinoma, sarcomas, melanoma, AIDS/Kaposi's Sarcoma, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy. The branch has an active autologous marrow infusion program.

The branch conducts weekly clinical conferences with the departments of radiation oncology, pathology, clinical pathology (hematology), and radiology on current problems and on the staging of lymphomas, Hodgkin's disease, and testicular carcinoma. Research focuses on the general areas of drug resistance and cytogenetics of neoplastic and hemopoietic cells, tumor immunology, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is under way in the field of hormone receptors, and the molecular biology of hormone action. The branch conducts weekly laboratory conferences on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI-Navy Medical Oncology Branch—

John D. Minna, M.D.

The NCI-Navy Medical Oncology Branch is located at the Naval Hospital Bethesda, (NHBETH) in Bethesda, Maryland across the street from the NIH Clinical Center. This branch is part of the NCI intramural Clinical Oncology Program and, with the Navy Hematology-Oncology Branch (John Phares, M.D., and Michael Anderson, M.D., Chiefs), part of the NHBETH cancer treatment program. The NHBETH is a 450 bed tertiary referral hospital for active duty military, military retired, and military dependents. Patients are referred from around the world with all types of malignant disease including solid tumors (e.g. lung, breast, gastrointestinal) and hematologic malignancies (Hodgkin's disease, nonHodgkin's lymphomas, and acute and chronic leukemias). There is a large population of young adults with such malignant diseases as germ cell tumors. The program has a 20-bed inpatient service, and also provides consultation in oncology and hematology to the NHBETH (approximately 40-60 active inpatients at any one time). In addition, civilian patients who are eligible for NCI studies can be admitted to the program for care and study. The NCI-Navy Medical Oncology and Navy Hematology-Oncology Branches represent a joint and integrated NCI-Navy effort in cancer patient care, clinical and laboratory investigation, and training in clinical oncology and hematology. More than 2,000 patients are followed by the NCI-Navy Program in

a study and primary care setting and each fellow has approximately 150 patients as his or her primary care responsibility. Most fellows spend 6 months at the Clinical Center, NIH, and 6 months at the NHBETH during the clinical year. The clinical research studies involve a wide variety of diseases and represent a collaboration between the intramural Clinical Oncology Program Branches and the NHBETH.

The laboratory investigations of the branch revolve around human tumor cell biology and molecular genetics. These include studies of cell culture, molecular genetics of gene structure, expression and regulation, production of monoclonal antibodies, identification of tumor cell growth factors and pathways of differentiation, and gene transfer techniques. Major efforts involve growing tumors from individual patients and selecting therapy after *in vitro* drug sensitivity testing and studies of dominant and recessive oncogenes, transcription factors and peptide hormone genes in human tumors. The program is designed to include clinical training and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals.

Pediatric Oncology Branch—

Philip A. Pizzo, M.D.

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma and neuroblastoma. Children and adolescents are accepted for treatment. The areas of clinical investigations that are stressed are chemotherapy with new or established agents and therapeutic and preventive techniques, including cytokines and biological response modifiers, applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 26 inpatient beds and an extensive outpatient department. The branch also has an extremely active teaching program, with weekly clinical and laboratory conferences and seminars. Fellows also spend an elective rotation at the Children's Hospital Medical Center

for additional hematology training. Candidates are eligible for Board certification in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and/or radiotherapeutic means, followed by experimental manipulation to prolong remission. Numerous phase I studies of investigational agents for cancer and children with AIDS are under way.

In the infectious disease program, therapeutic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient.

In the second and third year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on the cellular and molecular biology of pediatric neoplasms (particularly neuroblastoma and sarcomas); clinical pharmacology and pharmacokinetics; tumor immunology; host defense and immunoregulation.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—

Eli Glatstein, M.D.

The Radiation Oncology Branch of the National Cancer Institute offers a 3-year training program in radiation oncology. This program is organized in conjunction with the Uniformed Services University of the Health Sciences, through Walter Reed Army Medical Center and the Naval Hospital Bethesda (NHBETH) in Bethesda. The program calls for 18 months at the NCI, 9 months at Walter Reed, and 9 months at the Naval Hospital Bethesda.

The program emphasizes all aspects of patient care in radiation therapy with major emphasis on treatment planning and dosimetry. Experimental approaches are emphasized within the National Cancer Institute as part of prospective clinical trials; conventional treatment approaches are emphasized at

the military facilities. Work on radiation sensitizing compounds, radioprotecting compounds, intraoperative irradiation, and atypical fractionation schemes will be ongoing at NCI. Areas of investigation include primary breast cancer, carcinoma of the bladder, small cell carcinoma of the lung, lymphoma, Hodgkin's disease, gliomas, mycosis fungoides, soft tissue sarcomas, and pediatric neoplasms. Opportunities for study of a wider spectrum of conditions are available through the military hospitals, with special attention to head and neck cancer and gynecologic neoplasms. The emphasis at all institutions will be on combined modality approaches and on long-term follow-up to assess success and morbidity.

Preference will be shown to candidates who have completed all or part of training in another oncologic specialty. The director of training for the program is Eli Glatstein, M.D., Radiation Oncology Branch, National Cancer Institute. Interested individuals should contact him.

Surgery Branch—

Steven A. Rosenberg, M.D., Ph.D.

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen, including sarcomas, colorectal, breast, lung, and melanoma. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. The branch has pioneered in the use of adoptive cellular therapy plus Interleukin-2 in patients with cancer. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Developmental Therapeutics Program—

Michael R. Boyd, M.D., Ph.D.

Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to a programmed preclinical evaluation. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, acquisition and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and extramural program consisting of a Biochemistry and Pharmacology grants program, National Cooperative Drug Discovery groups, and an extensive contract-based procurement program.

Medical Staff Fellows

First-year medical staff fellows in the Clinical Oncology Program are eligible to work in the laboratories of the Developmental Therapeutics Program (DTP) for their second and third years of research training. The following paragraphs describe current projects from which medical staff fellows may elect to participate.

Laboratory of Biological Chemistry—

Richard L. Cysyk, Ph.D.

This laboratory brings together scientists who identify, as targets for drug design, cellular reactions that are critical to tumor cell survival and to the control of cell division and differentiation. Emphasis is placed on targets uncovered by recent advances in cell biology. Compounds are designed to interfere with these targets and are evaluated for biochemical and antitumor effectiveness. Pharmacologic information—plasma levels, tissue levels, mechanism of action, transport, and metabolism—is used for experimental chemotherapy and for preclinical evaluation of the agent. An important aspect of the selective toxicity of an agent is the effect of endogenous factors present *in vivo* that can modify the cytotoxic properties of an agent and thereby influence differential toxicity. This laboratory identifies

and quantitates such endogenous factors, when possible, and devises methods to manipulate them to enhance the chemotherapeutic effectiveness of cytotoxic compounds.

Laboratory of Biochemical Pharmacology—

David G. Johns, M.D., Ph.D.

The laboratory conducts an integrated program for the characterization of antitumor and antiretroviral (anti-AIDS) agents, implements basic research on mechanisms of antitumor and antiviral drug action and drug toxicity, and develops strategies for improving the clinical utility of new or existing anticancer and anti-AIDS drugs by overcoming resistance and/or by protection of normal tissues against toxicity. Effects of such agents are assessed in experimental model systems *in vitro* and *in vivo* and on a variety of potential subcellular sites, e.g., nucleic acids, nuclear proteins, microtubular proteins, and enzyme systems. Analytical methodology for *in vivo* studies with new agents is developed and, where warranted, biological studies with these agents are extended to the preclinical and Phase I (clinical pharmacology) stages. A wide range of methodologies is currently in use, including a variety of tissue culture techniques, assays of antiretroviral activity, instrumental analysis (HPLC, mass spectrometry, and NMR when required), affinity chromatography, DNA and RNA isolation and characterization hybridization, autoradiography, pharmacokinetic analysis, and enzyme characterization.

Laboratory of Molecular Pharmacology—

Kurt W. Kohn, M.D., Ph.D.

The Laboratory of Molecular Pharmacology is studying the mechanisms of action on anticancer drugs that attack DNA or DNA-related enzymes. The possibility is being investigated that drugs could be designed to react at specific DNA sites, depending on DNA sequence or genome structure, based on the premise that anticancer action by DNA-damaging agents may depend on where in the genome the damage tends to occur. Included in this study are various classes of bifunctional alkylating agents and platinum complexes that are capable for forming interstrand or intra-strand crosslinks. The repair of DNA lesions in various gene regions is also being investigated. A major aim is to understand what makes certain tumor cells

unusually sensitive or resistant to drugs, and to use this information to design more specific anticancer drugs. The techniques employed include quantitative determination of alkylation intensities at specific DNA sites by DNA sequencing gel electrophoresis and computer analysis of digitized densitometer scans, quantitative hybridization of electrophoretically fractionated DNA from drug-treated cells to determine the selectivity of reaction with specific gene regions, and DNA filter elution methods for estimating the extent of DNA damage in cells treated in the pharmacologic dose range. A second area of active investigation concerns drugs that act by inhibition of DNA topoisomerase enzymes. Included in this category are anthracyclines, DNA intercalating agents, epipodophyllotoxins and camptothecins. These drugs trap topoisomerase complexes with DNA; the sites on the genome where this tends to occur are being determined. Topoisomerases, including drug-resistant variant enzymes, are purified from various mammalian cells and characterized. The actions of the enzymes of various forms of circular DNA and the formation of trapped complexes are determined. DNA filter elution and immunologic techniques are used to study drug-susceptible topoisomerase reactions in cells, in order to relate these reactions to cytotoxicity and to the proliferation state of cells. A third area of active investigation is the regulation of the synthesis of chromosomal proteins, particularly variant histone proteins, in relation to the cell cycle or to proliferation state. Genes corresponding to variant histone species showing different modes of regulation during the cell cycle are cloned and sequenced, in order to identify the genomic signals related to the different modes of regulation. The metabolic regulation mechanisms are being investigated through measurements of histone synthesis rates and pool sizes.

Carl Kupfer, M.D.

Director

Robert B. Nussenblatt, M.D.

Clinical Director

Jin Kinoshita, Ph.D.

Scientific Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three medical staff fellows from those candidates who have completed an accredited 3-year ophthalmology program. Fellows spend time in both clinical and laboratory research including patient care activities.

In selection of medical staff fellows, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Biometry and Epidemiology Program—

Daniel G. Seigel, Sc.D.

The Biometry and Epidemiology Program conducts studies in the areas of clinical trials, natural history, and epidemiology.

The Clinical Trials Branch is currently responsible for three national multiclinic trials involving surgery, drugs, and photocoagulation, as treatments to prevent disease progression in patients with diabetic retinopathy. These studies include hundreds or thousands of patients, and combine the skills of ophthalmologists and biostatisticians. Data generated in these studies not only provide a base for treatment strategies, but permit investigation of factors other than treatment related to disease progression.

The Epidemiology Branch conducts studies of the prevalence and incidence of diseases of the eye in the general population, and of personal, environmental, genetic, and biologic factors in the population that may be related. Data

from these studies are used to generate and evaluate hypotheses about the causes of such diseases. Data from the Framingham Eye Study and the Health and Nutrition Examination Survey are being analyzed to explicate the risk factors for changes in the lens and retina. A major national case-control study to investigate factors related to the development of several eye diseases is underway, as well as a re-survey of the Framingham population for factors related to the incidence and natural history of cataract and age-related maculopathy.

Laboratory of Retinal Cell and Molecular Biology—

Gerald J. Chader, Ph.D.

Research in this laboratory is focused on the retina and its function as an integral part of the central nervous system. The process of photoreception is investigated as are other normal neuronal activities. In particular, the molecular biology of hereditary eye diseases such as retinitis pigmentosa (RP) and retinoblastoma are studied.

More specifically, the function of specific proteins, enzymes, and messengers involved in the visual process are being examined. These include 1) rhodopsin, the intrinsic membrane protein which responds to the initial photic stimulus; 2) cyclic GMP, which is the intracellular transducer in the light response; and 3) interphotoreceptor retinoid-binding protein (IRBP), an extracellular matrix glycolipoprotein which functions as a vitamin A transport vehicle between neural retina and pigment epithelium. Extensive work on the molecular biology and genetics of IRBP is in progress in the laboratory. Cloning and sequencing are in progress as well as work at the genomic DNA and chromosomal level.

In conjunction with the basic studies on retinal function, cell and molecular biology aspects of RP and retinoblastoma are being investigated, using human tissue, animal models, and tissue culture. Several important leads in the RP area are being followed, e.g., abnormalities in cyclic GMP metabolism and possible linkage with decreased IRBP production and secretion by the rod photoreceptor cell. In the case of retinoblastoma, cell adhesion, growth, and differentiation are being assessed in human retinoblastoma cell lines. In particular, the

origin of retinoblastoma is being pinpointed along with the potential of tumor cells to develop along neuronal, glial, and pigment epithelial pathways.

Laboratory of Mechanisms of Ocular Disease—

Jin Kinoshita, Ph.D.

This laboratory investigates the underlying reasons for transparency of the normal lens and for the development of cataracts. Lens proteins are being investigated in regard to their relationship to cataract development. The genetic influence on synthesis of lens proteins and on cataract development in the neonate is being intensively studied. Oxidative stress is thought to lead to cataract development and is being studied as well. The role of the enzyme aldose reductase in the cataract process is also under examination. It is thought that this enzyme may play a critical role in ocular complications of diabetes and is actively being studied.

Laboratory of Sensorimotor Research—

Robert Wurtz, Ph.D.

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visuo-motor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movements are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and sub-cortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanism by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain-damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the online laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

- Section on Neuro-ophthalmology

James Carl, M.D.

David G. Cogan, M.D.

Patients from the ophthalmic and neurologic service are being studied using advanced methods for computer analysis of eye movements, in conjunction with the Laboratory of Sensorimotor Research. The main emphasis of these studies is in correlating the deficits found in these patients with neuro-physiologic mechanisms of oculomotor control determined from primate studies.

Laboratory of Molecular and Developmental Biology—
Joram Piatigorsky, Ph.D.

This laboratory conducts basic research on cellular and molecular biology. Emphasis is given to molecular and developmental genetics. The research is designed to elucidate both normal and disease processes. Eye tissues are used as models

for general problems concerning cellular differentiation and gene expression. Particular attention is given to lens, crystallins, and oncogenes. Normal and pathogenic visual processes are also being related to the structure and function of genes. Techniques utilized include DNA cloning, sequencing, and introducing clonal genes into cultured cells and transgenic mice. Phospholipid metabolism—particularly at the cell membrane—is also under investigation in order to advance our knowledge of cellular differentiation and differential gene expression.

Laboratory of Ophthalmic Pathology—

Toichiro Kuwabara, M.D.

This laboratory conducts basic and applied research in structural and functional changes in the eye caused by disease and congenital abnormalities. The laboratory participates in the diagnosis of eye problems by performing pathological studies of diseased tissues removed from patients. The laboratory will conduct research utilizing the modern techniques available to uncover the cause and nature of eye diseases and will provide training opportunities in ophthalmic pathology.

The laboratory is actively engaged in research on uveitis, diabetic retinopathy, corneal dystrophies, and corneal wound healing. Considerable emphasis is placed on the application of DNA technology to the study of hereditary diseases that affect the eye such as gyrate atrophy, retinoblastoma, and cataracts.

Laboratory of Immunology—

Robert B. Nussenblatt, M.D.

Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular autoimmunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e., toxoplasmosis, pars planitis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of patients with ocular inflammatory disease to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell

activity, and macrophage responsiveness. Patients are, in addition, being sought for a controlled double masked study in the therapy of endogenous uveitis.

Experimental Immunology—Research directed by Dr. Igal Gery centers on the study of inflammatory diseases of the eye. Dr. Gery is studying models for human uveitis and the pathogenic processes of experimental autoimmune uveitis (EAU). EAU can be experimentally induced in animals by immunization with purified retinal proteins, notably, the S-antigen and the Interphotoreceptor Retinoid-Binding Protein (IRBP). It has been found that the diseases induced by the two retinal proteins are generally similar but also demonstrate some important differences. The pineal gland of the brain and its role in inflammatory diseases is also being studied. Study of the immunological relationship between the retina and the pineal is in progress.

Clinical Branch—

Robert B. Nussenblatt, M.D.

The branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment.

- Section on Ophthalmic Genetics and Pediatric Ophthalmology—

Muriel I. Kaiser, M.D.

Our current investigations include chemical, biochemical, electrophysiologic, psychophysical, and linkage analysis studies of hereditary retinal and pigment epithelial dystrophies. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, we have expanded our programs to more directly examine the pathogenesis of these disorders. Biochemical, immunologic and recombinant DNA studies of animal models, as well as studies of human tissue, are being developed in collaboration with other members of the clinical and basic research branches of the National Eye Institute. The night blindness syndromes, familial vascular

retinopathies, macular dystrophies, vitelliform disorders, basement membrane defects, vitreoretinopathies, juvenile retinosis and color deficiencies are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism, and abnormalities of the anterior chamber angle associated with glaucoma. There is an active participation in the Interinstitute Genetics Program and a variety of genetic conditions with ophthalmic manifestations are seen.

Bi-monthly genetic counseling is given to students at the Maryland School for the Blind.

- Section on Retinal and Vitreal Disease—

Monique Roy, M.D.

Retinal deteriorations—Clinical, biochemical, cell biological, and metabolic investigations are being conducted to define underlying mechanisms in diseases such as age-related macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest. The retinal pigment epithelium, its normal function, pathophysiology, and interrelationships are of special interest. Family studies of macular and retinal degenerations are emphasized. A controlled, double-masked clinical trial to test the value of antioxidants in preventing visual loss from age-related macular degeneration is under way.

Vascular diseases—Clinical investigations are being conducted in the underlying mechanisms of diabetic retinopathy and sickle cell retinopathy. A controlled, double-masked clinical trial to test the value of aldose reductase inhibitors in preventing progression of diabetic retinopathy is in progress.

Claude Lenfant, M.D.

Director

Edward D. Korn, Ph.D.

Director of Intramural Research

Harry R. Keiser, M.D.

Clinical Director

Candidates for research and clinical positions as medical staff fellows have only one interview in this Institute. Medical staff fellows are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the fellow and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each fellow will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the fellow's training and experience as well as desires.

Each medical staff fellow will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as medical staff fellows are for a minimum of 2 years with a third optional year. In the past, most fellows have elected to remain for 3 full years and have been accorded this privilege.

Appointments in Clinical Research

These appointments are designed to give physicians training in clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical fellowship will be

credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory during the previous 2 years of training and is satisfactory here.

Medical staff fellows will be responsible, under the guidance of investigators on the NHLBI staff, for the primary medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the five medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, hematology and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The fellow devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical*. No clinical responsibilities are required during the second or the optional third year for fellows who have chosen nonclinical laboratories.

Medical Staff Fellows in Surgery

The Surgery Branch appoints four to five fellows yearly for a 2-year period. The fellowship is designed to provide an intensive 9-month interval of clinical cardiac surgery and cardiology experience with extensive responsibilities for surgical care. Eight weeks are spent as a chief fellow responsible for all clinical activities; approximately 15 months are devoted to clinical and/or laboratory research under the supervision of preceptors of the fellows' selection. The formal educational program includes weekly branch conferences and lectures in pharmacology, pathophysiology and clinical research. Additionally, a Surgery-Cardiology cardiac catheterization conference is held weekly. A Surgery Branch mortality and morbidity conference is held monthly.

The laboratory opportunities are extensive and include large animal surgery, studies in cardiac physiology, biochemistry, pathology, cardiac function and metabolism, prosthetic heart

valves and cerebral metabolism and protection. Projects include both prospective clinical protocols as well as laboratory research.

The fellowship is restricted to those with excellent academic and clinical recommendations who have a full-time academic career as a goal. Candidates must have completed a minimum of 2 core years in an approved surgical residency training program, although 3 years of prior training are preferred. Interested candidates are encouraged to write to Richard E. Clark, M.D., Chief, Surgery Branch, NHLBI, Bldg. 10, Room 2N244, National Institutes of Health, Bethesda, MD 20892.

Appointments in Laboratory Research

These appointments are designed to give highly qualified physicians an opportunity to do either clinical or basic research in any area of the Institute under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NHLBI programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Staff Appointments

Laboratories within NHLBI sometimes have openings for medical staff fellows appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory.

Joint Endocrinology Training Program

Medical staff fellows from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The program provides clinical and research experience in a wide variety of endocrine and metabolic diseases and qualifies fellows for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity

consisting of 3-month rotations on the endocrine services of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the fellow will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds and seminars. The remainder of the fellow's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. No more than two NHLBI fellows may enter this program in any one year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate School of the Foundation for Advanced Education in the Sciences, Inc. Medical staff fellows are expected to take advantage of this academic work. (See Part Four, page 296.)

Clinical Research Branches

Cardiology Branch—

Stephen E. Epstein, M.D.

The Cardiology Branch is involved in a broad range of clinical and basic research efforts. One major effort is directed toward developing approaches to revascularize the ischemic heart. One approach tests the potential of methods to stimulate angiogenesis. Intensive studies to elucidate the basic cellular mechanisms controlling new blood vessel growth, as well as to determine in animal models of ischemia whether angiogenesis can be successfully enhanced, are under way. In a second approach to revascularization studies are designed to develop and test catheter-based techniques to remodel stenosed coronary arteries, employing lasers, atherectomy devices and stents. Other major efforts include studies to elucidate the clinical significance and cellular mechanisms responsible for myocardial ischemia caused by abnormal small intramural coronary arteries. Studies are conducted to determine the clinical implications of abnormalities of cardiac diastolic function, and to elucidate the determinants of irreversible heart failure in patients with aortic and mitral valvular disease. More effective therapeutic approaches to hypertrophic cardiomyopathy, and the underlying cellular abnormality responsible for cardiomyopathy are studied.

Clinical Hematology Branch—

Arthur W. Nienhuis, M.D.

The research activities in this branch are focused on the problems of red cell production, hemoglobin synthesis and hemoglobin function. Syndromes of bone marrow failure, chiefly aplastic anemia, are investigated. Stem cell function, cell-cell interactions, lymphocyte populations and their function, and the production of various hematopoietic factors are assayed by *in vitro* techniques to define the pathogenesis of bone marrow hypofunction. Experimental treatments under study include immunosuppressive and antiviral agents. Regulation of the several globin genes is studied in the context of developmental switches in the hemoglobin phenotype in man and other species. The study of gene expression in patients with thalassemia is directed toward definition of molecular defects that result in deficient hemoglobin synthesis in these syndromes. Various strategies are devised and tested with the long term goal of introducing functional genes into the erythroid cells of such patients. Treatment protocols include the evaluation of various cytotoxic drugs for their potential to stimulate fetal hemoglobin production in patients with thalassemia and sickle cell anemia.

Hypertension-Endocrine Branch—

Harry R. Keiser, M.D.

This branch researches hypertension. Research opportunities are offered ranging from basic biochemistry, physiology and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, renin-angiotensin-aldosterone system, prostaglandins, atrial natriuretic factors, and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin, histamine and peptides.

There is also a research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. Molecular biological, biochemical and pharmacological techniques are used.

Molecular Disease Branch—

H. Bryan Brewer, M.D.

Research is directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Biochemical studies take several approaches including protein chemistry, immunology, tissue culture, molecular biology and enzymology. Clinical research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemias and on kinetic analysis of the metabolic defects in patients with these diseases. Activities are integrated in such a way that medical staff fellows may wish to participate in collaborative research involving several different areas.

Pathology Branch—

William C. Roberts, M.D.

This branch studies morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include transmission and scanning electron microscopy.

Pulmonary Branch—

Ronald G. Crystal, M.D.

Research is directed toward understanding basic mechanisms in inflammatory and immune processes in health and disease, with emphasis on understanding the pathogenesis of disorders of the human lung. Most studies utilize biologic materials from humans, particularly those obtained at sites of disease. A broad range of laboratory approaches are utilized, with major emphasis on those of molecular biology.

Current areas of interest include proteases and antiproteases, with emphasis on defining mutations in the relevant genes and how these mutations cause human disease. Approaches are developed to treat antiprotease deficiency states, including the use of antiproteases produced using recombinant methods and the development of "gene therapy" in which normal antiprotease genes are inserted into the host genome. There is interest in the regulation of expression of genes involved in T-lymphocyte and macrophage activation. Ongoing studies relate selective use of specific T-cell antigen receptor gene elements in

human disease and the control of cell proliferation, regulation of production of lymphokines and monokines, and manipulation of gene expression to enhance or suppress deranged inflammatory and immune processes. Clinical problems studied include acquired diseases in which T-cells and macrophages play a dominant role.

Surgery Branch—

Richard E. Clark, M.D.

Clinical and laboratory programs investigate basic problems in: 1) prosthetic heart valves, 2) myocardial function and metabolism, 3) augmentation of blood flow and power in ischemic myocardium, 4) pulmonary hypertension, and 5) cerebral protection. Clinical programs include measurement of myocardial pH associated with new myocardial preservation techniques, pulmonary effects of cardiopulmonary bypass, biochemical changes and total body metabolism during cardiopulmonary bypass and coronary resistance in the postoperative interval. Projects in NMR, isolated heart preparations, valve testing, ventricular function and sonomicrometry and endothelial cell studies are under way. Multidisciplinary interactions and collaborations are encouraged. Didactic sessions include a guest lecturer program, research seminars, joint conferences with cardiology and individual training in computer analysis and statistical methods.

Basic Research Laboratories

Laboratory of Biochemical Genetics—

Marshall Nirenberg, Ph.D.

- **Section on Molecular Biology—**

Marshall Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry are studied, particularly those that pertain to the development of the nervous system. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Many monoclonal antibodies have been generated and are used as probes for synaptic and other antigens. Cultured cells are used in many studies. Research also is conducted on cyclic nucleotides, ion channels and cell recognition.

- Section on Macromolecules—

Alan Peterkofsky, Ph.D.

Studies of cellular control in *Escherichia coli* are under way. One area of interest concerns the control of the synthesis and metabolism of cyclic AMP in bacterial cells. Current information suggests that cyclic AMP concentrations in *E. coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells. The laboratory is using biochemical and recombinant DNA approaches to study the regulation of expression of the gene for adenylate cyclase as well as the factors that regulate the enzyme activity. Another focus of attention is the *E. coli* cyclic AMP receptor protein. Analyses of structure, function and repression mechanisms involving this protein are under way.

Laboratory of Biochemistry—

Earl R. Stadtman, Ph.D.

- Section on Enzymes—

Earl R. Stadtman, Ph.D.

Studies are concerned with the elucidation of various mechanisms of metabolic regulation, specifically, studies on the regulation of enzyme activities by allosteric interactions, by enzyme catalyzed covalent modification (phosphorylation, nucleotidylation, etc.) of interconvertible enzymes, and on the regulation of enzyme levels by changes in the rates of protein degradation mediated by mixed-function oxidase catalyzed inactivation of enzymes. These studies involve the isolation and characterization of key regulatory enzymes and of the enzymes which catalyze their covalent modification, oxidative inactivation and proteolytic degradation.

- Section on Intermediary Metabolism and Bioenergetics—

Thressa C. Stadtman, Ph.D.

Studies on the mechanisms of anaerobic metabolism of one-carbon compounds and amino acids and phosphorylation reactions coupled to the electron transfer process are under way. Selenium-dependent enzymes involved in these reactions are isolated and characterized. The mechanism of incorporation of selenocysteine directed by the UGA stop codon is investigated. Emphasis is also on the roles of various coenzymes (e.g., vitamin B₁₂ coenzyme, CoA, deazaflavins, quinones) and

electron transfer proteins such as molybdo-iron sulfur proteins and flavoproteins. The occurrence and roles of selenium in amino acid transfer nucleic acids are investigated.

- Section on Protein Chemistry—

Ann Ginsburg, Ph.D.

Studies on protein structure are directed toward understanding the roles of ligand binding and of protein-protein interactions in enzyme catalysis and regulation.

- Section on Signal Transduction

Sue Goo Rhee, Ph.D.

Studies are concerned primarily with intracellular events occurring when receptors are occupied by various calcium-mobilizing ligands. Regulatory mechanisms and specific roles of phosphoinositide-specific phospholipase C isozymes and inositol trisphosphate kinase are investigated.

- Section on Metabolic Regulation—

P. Boon Chock, Ph.D.

This section conducts physical, chemical, and molecular-biological studies on enzyme action and its regulation. The roles of covalent modification in metabolic regulation of enzymes are investigated. This involves the study of phosphatidylinositol-specific phospholipase C system, Ca(II)-calmodulin-dependent protein phosphatase, Mg(II)-ATP-dependent protein phosphatase and the ubiquitination/deubiquitination cascade. Theoretical and experimental approaches on the energy and signal transduction via electroconformational mechanism are studied. Studies are carried out to elucidate the mechanism of various interactions which involve metal ions and biomacromolecules.

Laboratory of Cardiac Energetics—

Robert S. Balaban, Ph.D.

The Laboratory of Cardiac Energetics studies the cellular and molecular processes of the heart *in vivo*. Research is focused on new methods for the prevention and treatment of heart disease.

The cytosolic mechanisms of cardiac energy conversion, blood flow and contractility are investigated. Studies on a variety of levels from isolated enzyme function to *in vivo* human biochemistry are under way. Nuclear magnetic imaging

(MRI) and optical spectroscopy techniques are used to study the cardiac and other organ biochemistry *in vivo* and *in vitro*. Techniques to produce multidimensional metabolic or functional “images” of tissues are investigated.

Laboratory of Cell Biology—

Edward D. Korn, Ph.D.

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

- **Section on Cellular Biochemistry and Ultrastructure—**

Edward D. Korn, Ph.D.

This section studies the biochemistry of actomyosin-dependent cell motility, the process involved in such diverse phenomena as ameboid movement, phagocytosis, cytokinesis and determination of cell shape. Research includes the mechanism of actin polymerization including the role of ATP hydrolysis in the polymerization process and the regulation of actin polymerization and actin filament organization through the interaction of monomeric and polymeric actin with other cell proteins. A second major activity is the study of the mechanism of the regulation of myosin filament formation and actomyosin ATPase activity by phosphorylation of heavy and light chains of myosins of non-muscle origin. Approaches to these problems include protein physical chemistry, kinetics, electron microscopy and molecular biology.

- **Section on Cellular Physiology—**

Evan Eisenberg, M.D., Ph.D.

Studies are under way on the function of a recently discovered family of cellular proteins known collectively as the 70 kDa heat shock proteins which apparently play a number of important roles in the cell. First they are involved in several membrane related processes. They play an important role in endocytosis acting to remove clathrin coats from endocytic vesicles prior to their fusion with other membranes in the cell; are involved in the excretion of the transferrin receptor from the red blood cell; and have recently been reported to be involved in the transfer of newly synthesized proteins into the lumen of the endoplasmic reticulum. In addition to their role

in membrane processes, they are one of the most prominent of the heat shock proteins occurring in both prokaryotic and eukaryotic cells when the cells are subjected to some form of stress such as an increase in temperature. In their multiple actions in the cell, the 70K proteins have been described as being "molecular chaperones," acting to stabilize proteins as they are synthesized and move about the cell. We are studying both the mammalian 70 kDa proteins, isolated from bovine brain, and the eight variants of the 70 kDa heat shock protein which occur in yeast. These latter studies enable us to apply the techniques of molecular biology to our overall aim of correlating the physiological function of these proteins with their biochemical properties.

- Section of Membrane Enzymology—
Richard W. Hendler, Ph.D.

This section studies enzyme systems that require organization on, or interaction with membranes in order to ensure their proper functioning. The structure and thermodynamic properties of the mammalian electron transport chain are investigated by use of spectrally monitored potentiometric titrations. The mechanisms of energy transduction are studied by use of ion-selective electrodes in a microcomputer-directed system which measures membrane potentials, electrochemical potentials for protons, and various ion fluxes in relationship to the ΔG changes which occur during electron transport and ATP formation.

Laboratory of Cellular Metabolism— Martha Vaughan, M.D.

- Section on Metabolic Regulation—
Martha Vaughan, M.D.
- Section on Biochemical Physiology—
Vincent C. Manganiello, M.D., Ph.D.
- Section on Molecular Mechanisms—
Joel Moss, M.D., Ph.D.

Mechanisms of transmembrane signalling by guanine nucleotide-binding (G) proteins that regulate many critical cellular processes are studied using techniques of molecular genetics, biochemistry and cell biology. Cyclic AMP synthesis by the adenyl cyclase catalytic unit (the target enzyme) is

controlled by stimulatory and inhibitory agonists (e.g., hormones, neurotransmitters) acting through cell surface receptors linked by either stimulatory (G_s) or inhibitory (G_i) G proteins. G proteins are also involved in receptor-mediated regulation of phospholipid metabolism, (e.g., inositol phosphate and prostaglandin production), ion flux, cyclic nucleotide degradation, and visual excitation. Signals generated by receptor-agonist interaction are transmitted to an intracellular target via the specific G protein. Some of these G proteins are substrates for bacterial toxins (e.g., pertussis toxin, cholera toxin) that alter G protein activity and thereby contribute to the pathogenesis of the disease (whooping cough, cholera, respectively). Guanine nucleotide-binding proteins participate in the activation of cholera toxin, cellular transformation, and perhaps infection by the human immunodeficiency virus. Areas of current interest include: 1) molecular biology: isolation of genes and cDNAs for G proteins; analysis of regulatory regions; mechanisms for alternative splicing; regulation of tissue-specific expression and synthesis during differentiation; *in vitro* mutagenesis with expression in *E. coli* and cultured cells; 2) membrane biochemistry: reconstitution of function with purified receptors and G proteins; identification of active sites with monoclonal and monospecific antibodies; modification of function by toxin-catalyzed ADP-ribosylation; 3) cell biology: effects of hormones and toxins on cyclic nucleotide content and arachidonate metabolism in cultured cells; regulation of G protein mRNA and synthesis; 4) protein chemistry: characterization of enzymes and substrates of the ADP-ribosylation cycle in animal cells; effects of ADP-ribosylation on enzyme function; regulatory properties of phosphodiesterases that degrade cyclic nucleotides.

Laboratory of Chemical Pharmacology—

James R. Gillette, Ph.D.

Michael A. Beaven, Ph.D.

• Section on Drug-Enzyme Interaction—

James R. Gillette, Ph.D.

Studies on various aspects of drug disposition including pharmacokinetics and the relationship between drug metabolism and drug toxicity are under way. Studies on understanding the mechanisms of drug metabolism by enzyme systems in

liver microsomes, and pharmacokinetic factors that govern the conversion of inert substances to alkylating agents and other biologically active metabolites.

- Section of Drug-Tissue Interaction—

Gopal Krishna, Ph.D.

This section studies the initial events occurring in cells as the result of a variety of drug cell interactions, including the role of cyclic nucleotides and calcium as mediators of hormone actions, cell function and disease. It also investigates the role of calcium and ATP in cell damage induced by drugs, such as adriamycin and daunomycin, in cardiac myocytes in culture. Various mechanisms in drug-induced Parkinson's disease, as well as drug induced liver injury, are investigated.

- Section on Cellular Pharmacology—

Michael A. Beaven, Ph.D.

This section studies immunological release and action of inflammatory mediators, especially in isolated cell systems. Current work includes studies of the role of Ca^{++} and inositol phospholipids in the mechanism of mast cell degranulation and of the specific roles of regulatory proteins involved in the transduction of stimulatory signals in mast cells. The proteins currently under study are the GTP-coupling proteins, phospholipase C, protein kinase C and myosin kinase. The techniques of molecular and cell biology are used to investigate these proteins at an intracellular (e.g., with permeabilized cells, isolated membranes, etc.), and molecular (e.g., with cell mutants with specific defects in signalling mechanisms) level. Although the primary focus is the mast cell (and cultured cell analogs), comparative studies are conducted with other cell models.

- Section on Pharmacological Chemistry—

Lance R. Pohl, Pharm. D., Ph.D.

The metabolic and immunologic basis of drug-induced hypersensitivities (allergies) and the mechanism and biological consequences of the interaction of radical metabolites of xenobiotics and endogenous compounds with heme proteins such as cytochromes P-450, myoglobin and hemoglobin are studied. Studies involve the isolation and characterization of drug-induced neoantigens and the investigation of their role in

immunopathology. The products of the interaction of radical metabolites with heme proteins, which include soluble heme products and covalently bound heme-derived products, are characterized and their mechanisms of formation and pharmacologic and toxicologic activities are characterized. Modern techniques of chemistry, biochemistry, immunology, cellular biology and molecular biology are applied.

Laboratory of Chemistry—

Henry M. Fales, Ph.D.

This laboratory investigates the physical and chemical properties of molecules with a view to elucidating their biochemical functions. Specialties are nuclear magnetic resonance, mass spectrometry, x-ray crystallography, chromatography, and laboratory computer applications. A special concern is the development of new techniques and their application to problems of current interest. Extensive collaborations are carried out with chemists, physicists, clinicians, biologists and computer specialists.

• Section on Chemical Structure—

Henry M. Fales, Ph.D.

The nuclear magnetic resonance group develops methods for carrying out studies of biologically important systems both *in vitro* and *in vivo* including cellular systems. Such studies involve conformation and activity of intermediate molecular weight peptides and small proteins, identification and characterization of metabolites *in vivo*, investigations of metabolic pathways and determinations of the related rates.

Mass spectrometric studies include gas liquid chromatographic analysis of trace amino acids, drug metabolites, urine components in diseased states, and insect and plant toxins. New methods are developed for applying the method to high molecular weight involatile substances and for elucidating structures of ions by controlling fragmentation.

The crystallographic work of the section consists of determining the structure at atomic resolution over the whole range of molecular weights at which such techniques are feasible. Results are interpreted in terms of physiological action and chemical behavior. Interpretation can include molecular mechanics and molecular orbital techniques. Recent examples include colchinoids, cyclic peptides related to actinomycin, metal

complexes in cancer therapy and carcinogens. The section is also interested in the development of computer programs for use in all areas of its research and in applications of the personal computer in the laboratory.

- Section on Structural Nuclear Magnetic Resonance—
Robert H. Highet, Ph.D.

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. These include the development of multidimensional pulse Fourier transform methods. Typical studies may include investigation of solution conformations, structures and equilibria of tautomers, and the identification of primary and secondary metabolites of animal and plant origin. The studies expand and utilize the structural dependence of NMR parameters.

Laboratory of Kidney and Electrolyte Metabolism

Maurice B. Burg, M.D.

- Section on Renal Cellular and Molecular Biology—
Maurice B. Burg, M.D.
- Section on Renal Mechanisms—
Mark Knepper, M.D.
- Section on Epithelial Transport—
Kenneth Spring, Ph.D.

This laboratory studies kidney function. The major objectives are to understand the basic processes at molecular and cellular levels, determine how they are controlled, and analyze how they are integrated to result in overall renal function. The areas emphasized include epithelial transport, cellular osmoregulation, metabolism related to transport, and hormonal responses. A number of preparations are utilized, such as intact kidneys, tubule suspensions, isolated perfused tubules, tissue cultures, and urinary bladders. The experimental approaches include nuclear magnetic resonance, quantitative microscopy, image analysis, electrophysiology, biochemistry, cell and molecular biology, and mathematical modelling.

Laboratory of Molecular Cardiology—

Robert S. Adelstein, M.D.

The regulation and function of the contractile proteins in muscle and nonmuscle cells are studied. The role of calcium, calmodulin and phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include the mechanism by which phosphorylation alters contractile activity in smooth muscle and nonmuscle cells, regulation of contractile protein expression in cultured smooth muscle cells and cloning the genes for selected contractile proteins. The role these proteins and their genes play in cellular development, differentiation, cell proliferation and tumorigenicity is studied.

Laboratory of Molecular Hematology—

W. French Anderson, M.D.

This laboratory studies the mechanism and regulation of mammalian gene expression, using immunodeficiency diseases and hemoglobin biosynthesis as primary models. The major objective is to develop the understanding and techniques necessary to carry out gene therapy for human genetic diseases. Major areas of research include: gene cloning and gene transfer, retroviral vector development, isolation and characterization of *trans* factors involved in gene expression.

Laboratory of Technical Development—

Robert L. Bowman, M.D.

This laboratory develops, then applies, instrumentation and methods useful in biomedical research. Included are new ways to separate and purify molecules and cells, ultramicrochemical techniques, picosecond laser-activated fluorescence spectroscopy, development of artificial organs, analysis of rapid chemical reactions with calorimetric and optical detection, electron spin resonance, new cell culture methods and practical clinical instruments.

• Section on Biophysical Instrumentation—

Robert L. Berger, Ph.D.

This section uses new physical, chemical, and computer science technology to develop new instruments and methods for the study of the mechanism of action of biological macromolecules particularly the chemical equilibria and kinetics as

these molecules react with ligands. Current work involves the development of highly sensitive batch, flow, titration and scanning, microcalorimeters, as well as a new family of fast flow devices for quench, stopped flow, and accelerated flow studies.

- Section on Pulmonary and Cardiac Assist Devices—
Theodor Kolobow, M.D.

This section conducts a program to develop and apply devices for extra corporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators; blood pumps, and control systems. We are exploring methods for optimal extracorporeal support of acutely failing respiratory and/or cardiac functions.

T. Franklin Williams, M.D.

Director

George R. Martin, Ph.D.

Scientific Director

Reubin Andres, M.D.

Clinical Director

Medical Staff Fellows

The Intramural Research Program of the National Institute on Aging (NIA) is comprised of eight Laboratories and two branches. Seven of these laboratories and both branches are located in Baltimore, Maryland at the Gerontology Research Center (GRC) on the campus of the Francis Scott Key Medical Center, a Johns Hopkins Medical Institution. The Laboratory of Neurosciences is located at the NIH in Bethesda.

At both locales, two year programs in both basic and clinical research are available with possible extensions up to three to seven years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a medical subspecialty board. Preference is given to candidates who intend to pursue careers in investigative and academic medicine.

In addition to these fellowship opportunities, combined clinical and research training programs are available with Johns Hopkins University and the Francis Scott Key Medical Center. For example, one or more years of clinical geriatrics or cardiology training at the JHU-FSK may be followed by two or more years at the GRC, NIA. This program requires dual acceptances by both institutions (JHU-FSK and GRC). The usual pattern is one year of clinical training followed by two years of research. Flexibility is possible, however, including the initiation of research activities during the clinical year and continuation of clinical activities during the research years. The research years may be spent in any of the seven GRC laboratories listed below in accord with the aptitudes, experience and career goals of the individual fellows.

Medical staff fellows are encouraged to participate in seminars conducted by the NIA Center's staff who present a comprehensive view of research in aging and related topics. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical physiological and behavioral investigation is the Baltimore Longitudinal Study of Aging. The research participants are volunteers who range in age from the late teen years into the 90s and reside in the community. They return for extensive studies every 2 years, spending 2½ days each visit, and are enrolled for their entire lives. The study of men is now of 31 years' duration; the study on women began in 1978. There are now over 1,000 active participants.

In addition to these Longitudinal Studies of normative aging and of mechanisms underlying age changes, studies of age-disease interactions are investigated at the JHU/FSK General Clinical Research Center; joint outpatient and in-patient studies may be conducted.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Extensive computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

Prospective candidates wishing further information should write to either George R. Martin, Ph.D., Scientific Director, or Reubin Andres, M.D., Clinical Director, NIA Gerontology Research Center, 4940 Eastern Avenue, Baltimore, MD 21224. Specific information about research opportunities in the Baltimore Longitudinal Study of Aging should be sent to James L. Fozard, Ph.D., at the above address. Prospective candidates wishing specific information about the Laboratory of Neurosciences should write to Mark Schapiro, M.D., Clinical Section, NIA, Building 10, Room 6C414, Bethesda, MD 20892 or to Stanley I. Rapoport, M.D., Chief, Laboratory of Neurosciences, NIA, Building 10, Room 6C103, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIA programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Research Branches and Laboratories

Longitudinal Studies Branch—

James L. Fozard, Ph.D.

This branch conducts and collaborates with other Center units on longitudinal research dealing with normal human aging in relation to a variety of physiological and behavioral functions. Areas of research include age changes in sensory and perceptual functions such as vision, hearing, taste and smell; oral physiology; pulmonary function; response speed; clinical assessments of health and disease; risk factor analyses of morbidity and mortality; and a variety of studies into the epidemiology of aging.

Laboratory of Clinical Physiology—

Reubin Andres, M.D.

This laboratory is concerned primarily with studies on physiologic changes occurring over the entire adult lifespan. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- **Endocrinology Section—**

S. Mitchell Harman, M.D. (Acting)

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and neuroendocrinology. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on tissues from a variety of organs; cell culture techniques are used with hormone-sensitive and producing cells, especially of adipose and pituitary origin.

- **Metabolism Section—**

Reubin Andres, M.D.

This section emphasizes clinical research on such metabolic variables as: glucose-insulin homeostatic mechanisms and

diabetes mellitus; serum lipids, the hyperlipidemias, and adipose tissue metabolism; obesity, patterns of fat distribution, and body composition; acute and sustained effects of physical activity; dietary and nutritional evaluation; the interactive effects of these variables on rates of aging, on disease development, and on longevity. There is close collaboration of this section with the Research Program of the Geriatric Division at FSK under Dr. Andrew Goldberg.

- Clinical Immunology Section—
William H. Adler, M.D.

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigations of the mechanisms of these deficiencies in humans and experimental animals.

- Applied Physiology Section--
Jordan D. Tobin, M.D.

Investigators in this unit study age changes in human beings in specific systems including renal, bone and musculoskeletal. They investigate interrelationships between age effects in different organ systems and in overall physiological changes in individuals. Efforts are made to differentiate between pathological disease changes and those secondary to pure age effects. Others in this section develop and adapt computer techniques for kinetic modeling of physiological systems for the analysis of longitudinal data.

Laboratory of Behavioral Sciences—

Bernard T. Engel, Ph.D.

This Laboratory conducts clinical research on the application of behavioral methods and principles in the assessment, control, and treatment of age-related medical disorders.

- Behavioral Medicine Section—
David E. Anderson, Ph.D.

Studies focus on environmental and behavioral control of physiological functions relevant to health and disease in the aging. Laboratory studies are concerned with the effects of breathing patterns on blood pressure, cardiac and vascular

functions in normal subjects and in patients with specific cardiovascular disorders (hypertension, transient ischemias, atrial fibrillation) and pulmonary (chronic obstructive lung disease, sleep apnea) disorders. Field studies focus on ambulatory monitoring of cardiovascular functions in the natural environment as these relate to behavior, diet and stress management.

- Behavioral Physiology Section—
Bernard T. Engel, Ph.D.

Researchers in this section conduct basic studies in appropriate animal models on the mechanisms mediating the interactions between behavioral factors such as learning or discrimination, and physiological or biochemical factors such as the cardiovascular or pulmonary adjustments to exercise or to cold stress. Others study the influence of aging on the interaction between behavioral and physiological processes.

Laboratory of Personality and Cognition—

Paul T. Costa, Ph.D.

This laboratory emphasizes basic and clinical studies of individual differences in cognitive and personality processes and traits. It also investigates the influence of age on these variables and their reciprocal influence on health, well-being and adaptation. The laboratory employs longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and health-care needs, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

- Cognition Section—
David L. Arenberg, Ph.D.

Researchers in this section study the psychological mechanisms underlying age-related changes in memory, learning and reasoning. They seek to determine age-associated changes in verbal learning, memory, problem-solving, information processing, and the relationships between conscious and unconscious information processing. In addition, they analyze the roles of psychological and physiological characteristics in age differences and age changes in cognitive performance.

- **Personality, Stress and Coping Section—**

Paul T. Costa, Ph.D.

This section deals with the dimensions of personality and their influence on processes of adaptation in adult men and women. They determine methods and strategies for coping with the stresses of adult life and evaluate the effects of different coping mechanisms as personality dispositions on such outcomes as subjective well-being, social functioning and physical and psychiatric health. The investigators use epidemiological and longitudinal analyses of personality dimensions to study the interactions of aging with personality and psychological processes.

- **Laboratory of Cardiovascular Sciences—**

Edward G. Lakatta, M.D.

Scientists in this laboratory conceptualize and implement original research to identify and characterize the basic mechanisms that control myocardial function. These studies are subsequently extended to describe the influence of age and age-related chronic pathologic conditions in studies conducted both in man and in animal models; the latter involve isolated cardiac muscle, myocytes and subcellular organelles.

- **Cardiac Function Section—**

Edward G. Lakatta, M.D.

This section emphasizes research on cardiac dynamics and basic studies in isolated myocardial cells. Researchers describe the influence of age and age-related chronic pathological conditions in the intact cardiovascular system with special attention to the human myocardium. They normally use noninvasive methodology (e.g., echocardiography, gated blood pool scans, pharmacological probes, and stress). The mechanisms that govern excitation and contraction of myocardial cells are investigated with state-of-the-art techniques that allow the simultaneous recording of contractility, cytosolic $[Ca^{++}]$ and membrane potential or current in a single myocyte. These studies are complemented by experiments in the isolated heart and by biochemical measurements. These techniques are used to characterize the mechanisms that control myocardial function and to study the impact of aging and chronic disease states on these mechanisms.

- **Energy Metabolism and Bioenergetics Section—**
Richard G. Hansford, Ph.D.

These investigators study the regulation of substrate oxidation responsible for providing energy in heart muscle and other excitable tissues, as well as the derangement of these central mechanisms which may occur in old age. A special concern is the role of calcium ion as a messenger in this regulation, and the homeostasis of cytoplasmic calcium ion concentration. Isolated cells, nerve terminals, mitochondria, enzymes are the principal objects of these studies.

Laboratory of Molecular Genetics—

George R. Martin, Ph.D. (Acting)

This laboratory conducts research on the fundamental nature of aging at the molecular level. It investigates changes in gene structure and function with aging. Researchers utilize the techniques of molecular genetics to examine age-related alterations in cellular function, and identify, isolate, and characterize genes involved in aging processes and in age-dependent disorders.

Laboratory of Biological Chemistry—

Jeffrey Froehlich, M.D. (Acting)

This laboratory carries out novel, rigorous biochemical investigations to describe the mechanisms underlying biological processes influenced by age and age-related pathologic states. Studies are focused on signal transduction mechanisms and the expression of hormones, growth factors and pharmacological agents in regulating ion transport, growth and differentiation, metabolism, and intra- and intercellular communication.

- **Regulatory Mechanisms Section—**
Jeffrey Froehlich, M.D. (Acting)

This section investigates, at the cellular and molecular levels, the mechanisms by which ion transport, metabolism, acid-base balance, cell-cell interactions, and growth and differentiation are controlled. An important focus of this research is on mineral metabolism of bone, kidney and intestinal cells, the actions of calcitropic and phosphatropic hormones, and age-associated involutional osteoporosis. Membranal reception of endocrines,

signal transduction systems, and cellular responses to hormones relevant to the aging process and age-related disorders are studied.

- Membrane Biology Section—

Jeffrey Froehlich, M.D.

This section seeks to determine the chemical nature and sequence of intermediate reactions controlling the movement of cations through ionic channels and pumps. The behavior of these systems with respect to energy utilization and energy transduction, ion selectivity, gating mechanisms, and sensitivity to hormones and pharmacological agents is characterized. Studies concern how the affinity, capacity, and selectivity of ion translocation mechanisms are affected by aging.

Laboratory of Cellular and Molecular Biology—

Gunther L. Eichhorn, Ph.D.

This laboratory combines studies on the biochemistry of aging with studies on the mechanism of fundamental biochemical events that are important in the aging process. Present studies include research into the mechanism of RNA synthesis, as well as hormone therapy, age changes in molecular dynamics, and non-invasive magnetic resonance studies of aging in animals and humans.

- Inorganic Biochemistry Section—

Gunther L. Eichhorn, Ph.D.

This section is probing the structure of the active site of RNA polymerase in order to understand of mechanism of RNA synthesis. Studies are carried out on the effects of conformational changes in DNA, particularly those induced by metal ions, on genetic information transfer. Effects of metals on aging and Alzheimer's disease are studied. Magnetic resonance is employed for *in vivo* studies of age changes in animals and humans using both spectroscopic and imaging techniques.

- Molecular Physiology and Genetics Section—

George S. Roth, Ph.D.

Studies are carried out on the regulation of physiological and behavioral functions during aging, especially those most critical to life maintenance, as influenced by endocrine, neuro-endocrine, nutritional, environmental, and genetic factors.

Particular emphasis is placed on elucidating the molecular and biochemical age changes which occur in the regulatory processes.

- **Macromolecular Chemistry Section—**

Josef Pitha, Ph.D.

Experimental therapy of diseases accompanying human aging is the main interest in this section. Compounds which selectively destroy neurotransmitter receptors in living animals without cellular toxicity were designed, prepared and are currently studied; the receptor lesion can be created selectively either in the brain or the periphery. In another project nontoxic solubilizers of lipid-soluble vitamins and of steroids were developed and have been used (a) to make preparations of sex hormones which are effective upon oral administration and (b) to develop an analog of complexation therapy (currently used in metal poisoning) which would be applicable to the problems arising from lipophilic pathogens.

- **Molecular Dynamics Section—**

Joseph M. Rifkind, Ph.D.

Research in this section is directed at the role of oxygen in biological systems and how it influences the aging process. Both the requirement for regulated transport to deliver oxygen to the tissues necessary for metabolic needs and the detrimental effects of certain activated oxygen species are studied. Oxygen transport studies seek to understand the binding of oxygen to hemoglobin and how cellular metabolism and membrane interactions regulate the uptake and release of oxygen from the erythrocytes. The generation of oxyradicals associated with the oxidation of hemoglobin, occurring continuously even *in vivo*, is studied, as is the leakage of such potentially dangerous radicals from the erythrocytes under oxidative stress and possible damage to tissues and cells.

Laboratory of Neurosciences—

Stanley I. Rapoport, M.D.

This laboratory investigates the function, structure, physiology, and pharmacology of the nervous system, and changes that take place during development, aging and disease, in animal models and in man.

- Cerebral Physiology and Metabolism Section—
Stanley I. Rapoport, M.D.

This section conducts fundamental research on animal models of aging and disease. Areas of concern include neuropharmacology and pharmacokinetics; the blood-brain barrier (structure, transport and permeability); peripheral nerve function; cerebral metabolism; electrophysiological properties of neurons in culture; molecular biology (gene expression, in situ hybridization). Methods include whole animal preparations, tissue culture, electrophysiology (current and patch clamping), analytical techniques (HPLC, gas chromatography, mass spectrometry); quantitative autoradiography (regional cerebral blood flow, glucose metabolism, lipid metabolism); radiotracer techniques and modeling; electron-microscopy.

- Brain Aging and Dementia Section—
Robert P. Friedland, M.D.

This section operates an 8-bed Patient Care Unit at the Clinical Center, as well as an outpatient clinic on Dementia and Depression (for recruitment and conducting outpatient studies). Physicians, neuropsychologists, pharmacologists and engineers work together on aging of the central nervous system in healthy men and women between the ages of 18 and 90 years, dementia (multiple infarct, Alzheimer's), Down syndrome, hypertension, depression, extrapyramidal disorders, and associated neurological diseases related to the elderly. Studies are longitudinal with eventual postmortem followup. Methods employed include neuropsychometrics, biochemical analysis of neurotransmitters and metabolites in cerebrospinal fluid, positron emission tomography to examine cerebral metabolism and receptor binding, and magnetic image resonance and computer assisted tomography to examine brain morphology. Emphasis is placed on elucidating the physiology and pathology of the brain aging and disease.

- Unit on Clinical Pharmacology and Pharmacokinetics—
Timothy Soncrant, M.D.

This unit, integrated with the Clinical Program, examines behavioral, cognitive and motor effects of centrally acting drugs, as well as metabolic effects using positron emission tomography. The measurements are related to peripheral and

central pharmacokinetics. The aim is to understand the imbalances of neurotransmitter functions in various aging and disease states, and to examine therapeutic action of appropriate drugs.

National Institute on Alcohol Abuse and Alcoholism

Enoch Gordis, M.D.

Director

Boris Tabakoff, Ph.D.

Scientific Director

Markku Linnoila, M.D., Ph.D.

Clinical Director

Alcohol, Drug Abuse, and Mental Health Administration

The National Institute on Alcohol Abuse and Alcoholism conducts an intramural program of basic and applied research on the multiple determinants and processes of alcoholism and other alcohol-derived health problems. The clinical facilities and research laboratories are located at the National Institutes of Health Clinical Center in Bethesda, Maryland. Medical staff fellow appointments are available to conduct clinical and/or basic research investigations. Depending upon the appointment, certain fellows will also have clinical responsibilities.

Appointments in Clinical Research

Medical staff fellowship positions are available in neurology, internal medicine, psychiatry, experimental therapeutics, and developmental neurology. Fellows are appointed for 2 years with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on the NIAAA ward and involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NIAAA research emphases.

Candidates requiring further information about the clinical positions for medical staff fellows should write to Markku Linnoila, M.D., Ph.D., Clinical Director, DICBR, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3B19, National Institutes of Health, Bethesda, Maryland 20892.

Appointments in Laboratory Research

NIAAA medical staff fellow positions are available for laboratory research in the Laboratory of Clinical Studies, the Laboratory of Metabolism and Molecular Biology, and the Laboratory of Physiologic and Pharmacologic Studies.

Appointments are for a 2-year period, with the possibility of extension.

Fellows will engage in research on contemporary biomedical problems. During their tenure, fellows will devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Research experience is gained through the process of personal guidance by senior scientists who are preceptors. Areas of study are developed by each fellow in conjunction with the preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned.

Medical staff fellows have the opportunity to work closely with a diverse group of senior investigators, to participate in courses, conferences and seminars, and to employ advanced research methodologies in the course of their research.

For further information on the NIAAA Medical Staff Fellowship Program, write to Boris Tabakoff, Ph.D., Scientific Director, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3C103, Bethesda, Maryland 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIAAA programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Unit for Special Projects, Office of the Scientific Director—

Boris Tabakoff, Ph.D.

The Unit for Special Projects concentrates its efforts on problems related to the biochemical determinants of behavior and behavioral genetics. A selective breeding program for drug-induced neuroadaptation in rodents is under way. Neural mechanisms for development of tolerance to alcohol and other sedative hypnotics are being examined by molecular genetic, autoradiographic, and enzymatic techniques. Cell surface receptors for peptide hormones and immunologically active

peptides are being examined, and the coupling of peptide recognition sites to intracellular events, such as generation of cyclic nucleotide and calcium homeostasis, is being studied.

Laboratory of Clinical Studies—

Markku Linnoila, M.D., Ph.D.

The Laboratory of Clinical Studies is composed of six sections: the Section of Clinical Science (Theodore George, M.D.), Section of Clinical Brain Research (Michael Eckardt, Ph.D.), Section of Clinical Pharmacology, Section of Analytical Chemistry (Norman Salem, Jr., Ph.D.), Section of Genetic Studies (David Goldman, M.D.), and the Unit of Family Studies (Debra Garnett, M.S.W.).

The major research interests of the laboratory concern effects of acute and chronic consumption of alcohol in humans. Furthermore, blood relatives of alcoholics at a high risk of developing alcoholism will be compared to age and sex matched subjects without a family history of excessive drinking or alcoholism. The techniques available include medical, psychiatric and psychometric evaluation of patients and their families, EEG-telemetry, sleep recording, activity and temperature monitoring, evoked responses, brain imaging, neuropsychological testing, drug concentration measurements with liquid chromatography, monoamine and neuropeptide analyses with liquid chromatography, membrane lipid analyses with mass fragmentography, receptor studies, animal behavioral pharmacology and molecular biology of alcoholism and aggressive behaviors. The aims of the program are to test and develop new approaches for the treatment and prevention of alcoholism and its complications, as well as to train professionals to work successfully in the field of alcohol research.

Laboratory of Metabolism and Molecular Biology—

Richard L. Veech, M.D., D. Phil.

The Laboratory of Metabolism and Molecular Biology is composed of three sections: the Section of Metabolic Control (Richard L. Veech, M.D., D. Phil.), Physical Chemistry (Alan McLaughlin, Ph.D.), and the Section on Molecular Genetics (Joseph P. Casazza, Ph.D.).

The laboratory's three sections reflect broad areas of biochemical and chemical expertise: 1) concentrates on questions

of the control of metabolic processes with a gamut of *in vivo* and *in vitro* techniques with a strong emphasis on analytical chemistry, enzyme kinetics and thermodynamics; 2) concentrates on the application of physical techniques, particularly ^{31}NMR , to the study of whole organs and isolated systems. Other areas of study in this section include physical-chemical analysis of cell membranes using NMR and other spectroscopic techniques; 3) uses the techniques of classical molecular biology, including cloning and site-directed mutagenesis, to investigate a variety of genetic disorders and disease states. Close collaboration between the sections offers fellows the opportunity to learn a wide variety of powerful techniques by working directly with senior scientists with wide experience in their particular methodology using the most up-to-date equipment.

Laboratory of Physiologic and Pharmacologic Studies—
George Kunos, M.D., Ph.D.

The Laboratory of Physiologic and Pharmacologic Studies is composed of the Office of the Chief and three sections: The Section on Receptor Mechanisms (Paula L. Hoffman, Ph.D.), the Section on Electrophysiology (Forrest F. Weight, M.D.), and the Section on Immunology (Randall L. Kincaid, Ph.D.).

Research in the laboratory is concerned with mechanisms of neurotransmitter and hormone action, with particular emphasis on receptor and signal transduction mechanisms. Within these broad areas, the Office of the Chief investigates the molecular pharmacology and mechanisms of regulation of adrenergic receptors, as well as the role of certain neurotransmitter systems in the CNS in the cardiovascular regulation and in the cardiovascular effects of ethanol. The Section on Receptor Mechanisms investigates receptor and receptor-effector coupling mechanisms at the molecular level to assess the role of changes in these systems in neuroadaptation to ethanol (tolerance and physical dependence). The Section on Electrophysiology uses voltage- and patch-clamp techniques to study the ionic basis of membrane permeability changes involved in the action of transmitters and neuroactive drugs including ethanol. The Section on Immunology studies the interactive roles of cyclic nucleotides, phosphoprotein metabolism and calmodulin in signal transduction in lymphoid and neural tissues, as well

as studying questions related to immune cell differentiation and developmental neurobiology. To address questions in the above areas, investigators of the laboratory use a variety of approaches ranging from the assessment of physiological functions in intact animals, through measurement of electrophysiological and biochemical responses in isolated cells or subcellular preparations, to using immunological and molecular biological techniques.

Anthony S. Fauci, M.D.

Director

John I. Gallin, M.D.

Director, Intramural Research Program

Michael M. Frank, M.D.

Clinical Director

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints medical staff fellows for the laboratories described below. Medical staff fellows in the Laboratory of Clinical Investigation and Laboratory of Immunoregulation begin after at least two years of training as a house officer. Fellowship appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation and Laboratory of Immunoregulation carry responsibility for patients in the research program but are not otherwise different from the other research positions.

Specific answers to any questions or additional information may be obtained by applicants from the Director, Intramural Research Program, NIAID, National Institutes of Health, Bethesda, MD 20892. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. Please be as specific as possible as to interests and information desired.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIAID programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Clinical Branches

Laboratory of Clinical Investigation—

Michael M. Frank, M.D.

Laboratory of Immunoregulation—

Anthony S. Fauci, M.D.

The NIAID appoints approximately 9 medical staff fellows. Appointments are made for 3 years and consist of a first year devoted mostly to the care of patients with immunologic, allergic, and infectious diseases and a second and third year devoted primarily to laboratory-based research.

The clinical period is integrated with a program in Clinical Allergy and Immunology that leads to Board eligibility for the American Board of Allergy and Immunology, a conjoint Board of Internal Medicine and Pediatrics. In addition, fellows already certified by the American Board of Internal Medicine may elect to take clinical training in infectious disease that leads to eligibility for the Infectious Disease sub-specialty board of the American Board of Internal Medicine. These programs include exposure to patients with a wide variety of immunologic, allergic, or infectious diseases on the 52-bed NIAID service of the Clinical Center. Clinical experience includes rotations at affiliated hospitals and clinics as well as an extensive formal teaching program involving lecture/seminar series and individual one-on-one teaching. Approximately 7 of the medical staff fellows are appointed to the Laboratory of Clinical Investigation and 2 of the fellows are appointed to the Laboratory of Immunoregulation. The clinical responsibilities are identical for fellows in both laboratories.

The laboratory period consists of a prolonged period of training in one of the research areas currently being pursued in the laboratory. This is under the general preceptorships of the laboratory chief and the senior members of the staff (listed below). Emphasis is placed on the mastery of the knowledge and techniques necessary for a career in basic investigation of diseases.

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

Laboratory of Clinical Investigation

- The genomic organization expression, mechanisms of latency and pathogenesis of human herpes virus infections.
- Molecular interactions between human immunodeficiency virus and herpes viruses.
- The role of host defense mechanisms in prevention of infections.
- Pathophysiology and treatment of autoimmune hemolytic anemia.
- Pathophysiology and treatment of hereditary angioedema.

- The pathophysiology and host defense response to bacteremia.
- Host defense mechanisms diagnosis and therapy of systemic mycoses.
- The role of the phagocytic cells in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Cellular and molecular mechanisms of immune regulation.
- The biochemical response and molecular biology of lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma, allergic diseases such as anaphylaxis, and allergic rhinosinusitis and food allergy.
- The role of immune complexes in the production of disease.
- The pathophysiology and treatment of systemic mastocytosis.
- Some aspects of immunopathologic mechanisms in parasitic infections.
- Laboratory and clinical evaluation of antiviral drugs.
- Mechanisms of regulation of mucosal immune responses.
- The pathogenesis of inflammatory bowel diseases.
- Molecular mechanisms responsible for the development of immunodeficiency diseases.
- The diagnosis and effective management of systemic mastocytosis.

Laboratory of Immunoregulation

- The regulation of human immune responses in normals and in diseases characterized by abnormalities of immune function. Studies include cellular and humoral components, cloning technology, receptor physiology, and molecular biology.
- Study of the immunopathogenic features of immune-mediated diseases and host defense defects.
- Clinical, immunopathogenic, and therapeutic features of the vasculitis syndromes.

- Studies of the clinical manifestations, virology, immunopathogenesis, molecular biology, and therapeutic aspects including immunological reconstitution of the acquired immunodeficiency syndrome (AIDS).
- The molecular biologic approach to gene activation and immunoregulation.
- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.
- The effect of corticosteroids and cytotoxic agents on lymphocyte sub-populations.

Further information can be obtained if inquiries with specific questions are addressed to Clinical Director, NIAID.

Research Areas and Senior Staff

Laboratory of Clinical Investigation—

Allergic Diseases—

Michael A. Kaliner, M.D., and

Robert Hohman, Ph.D.

Bacterial Diseases—

John I. Gallin, M.D., and

Harry L. Malech, M.D.

Clinical Immunology—

Michael M. Frank, M.D.

Louis Fries, M.D.

Keith Joiner, M.D., and

Carl Hammer, Ph.D.

Clinical Mycology—

John E. Bennett, M.D., and

Kyung J. Kwon-Chung, Ph.D.

Clinical Parasitology—

Franklin A. Neva, M.D.

Eric A. Ottesen, M.D., and

Theodore Nash, M.D.

Mast Cell Physiology—

Dean D. Metcalfe, M.D.

Medical Virology—

Stephen Straus, M.D., and

Jeffrey Ostrove, Ph.D.

Mucosal Immunity—

Warren Strober, M.D., and

Stephen P. James, M.D.

Laboratory of Immunoregulation—
Immunoregulation—

Anthony S. Fauci, M.D.
Scott Koenig, M.D., Ph.D.
Randi Y. Leavitt, M.D., Ph.D.
Gary S. Hoffman, M.D.
Ulrich K. Siebenlist, Ph.D.
Peter Bressler, M.D.
Ljubisa Vitkovic, Ph.D.
Julian L. Ambrus, Jr., M.D., and
John H. Kehrl, M.D.
Steven Schnittman, M.D.
Andrew Dayton, M.D., Ph.D.

AIDS Clinical Studies—

H. Clifford Lane, M.D.
Joseph A. Kovacs, M.D., and
Richard Davey, M.D.

**Basic Research
Laboratories**

Laboratory of Viral Diseases—

Bernard Moss, M.D., Ph.D.

Members of the laboratory conduct basic research on the genetic organization, expression, replication, assembly, immunology and pathogenicity of viruses. In addition, live recombinant viruses are being genetically engineered for use as immunological tools and as vaccines against a variety of infectious agents. Current research topics include:

- Regulation of gene expression *in vitro* and *in vivo*
- Mechanisms of DNA replication *in vitro* and *in vivo*
- Structure and function of RNA and DNA polymerases
- Genetic engineering of recombinant viruses as live vaccines
- Antiviral agents
- Determinants of virus virulence
- Host resistance genes
- Viral growth factors
- Targets of humoral and cell-mediated immunity

After discussions with members of the laboratory, Medical Staff Fellows choose a research topic and develop experimental protocols. Training in areas of molecular biology, recombinant

DNA technology, enzymology, protein chemistry, immunology, tissue culture, and virology is provided during the course of investigations. Progress is monitored informally and by weekly research meetings of the laboratory staff.

Research Areas and Senior Staff

Gene Expression—

Bernard Moss, M.D., Ph.D., and
James Rose, M.D.

DNA Replication—

Mark Challberg, Ph.D., and
Frank DeFilippes, Ph.D.

Viral Immunology—

Jack Bennink, Ph.D., and
John Yewdell, M.D.

Virus Pathogenesis—

Mark Buller, Ph.D.

Laboratory of Infectious Diseases—

Robert M. Chanock, M.D.

This laboratory's activities are concerned with the basic behavior of viral pathogens that play an important role in acute infectious diseases of man. The importance, disease manifestations, and immunological properties of various respiratory tract, gastrointestinal tract, and hepatic viral pathogens are defined during the study of experimentally-infected animals or individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers. Special emphasis is given to the factors involved in the hosts' resistance to both infection and illness. The techniques of molecular biology and microbial genetics are employed to study the nature of virulence. These techniques are also utilized to construct recombinant or reassortant viruses and to select attenuated mutants which are subsequently evaluated for their usefulness in immunization against natural disease.

Biophysical techniques, including immune electron microscopy, are used to define the subparticulate structure of viruses and to search for fastidious viruses, such as those responsible for acute gastroenteritis and hepatitis which cannot be detected in standard tissue culture systems. Appointees can

expect to receive training in basic biophysical and molecular biological characterization of viruses, microbial genetics, immunologic methods used in the study of viral diseases, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff

Epidemiology—

Albert Z. Kapikian, M.D.

Hepatitis Virus—

Robert H. Purcell, M.D.

Molecular Viral Biology—

Ching-Juh Lai, Ph.D.

Respiratory Viruses—

Brian Murphy, Ph.D.

Laboratory of Immunogenetics—

Thomas J. Kindt, Ph.D.

This group is involved in basic research on major gene complexes important in immune function. The approaches used in these studies emphasize structural, serologic, and molecular genetic investigations. The techniques used include quantitative radioimmunoassays, protein structure determinations, recombinant DNA technologies including gene cloning and nucleotide sequencing, DNA mediated gene transfer into mammalian cells; preparation and study of T- and B-cell hybridomas, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on cloning, sequencing, and genetic analyses of genes for rabbit T-cell antigen receptors and MHC products; the use of the rabbit as a model for human retroviral diseases including HTLV-1 and HIV-1; the effect of retroviral infection on immune function in the rabbit; structural and functional studies on human HLA antigens; assembly and function of HLA class II antigens and regulation of the class II gene family; genetic studies of human T-cell receptor genes and their role in disease susceptibility.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry and molecular biology and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of current concepts concerning the molecular basis of the immune response.

Research Areas and Senior Staff

MHC and TcR Genetics—

T. J. Kindt, Ph.D.

Molecular Immunogenetics—

E. O. Long, Ph.D.

M.A. Robinson, Ph.D.

Laboratory of Immunology—

William E. Paul, M.D.

Scientists in the Laboratory of Immunology are engaged in the study of various aspects of cellular, molecular, and developmental biology of lymphocytes; the regulation of immune responses; immunogenetics; and immunochemistry. Emphasis is placed on developing an understanding of how the various elements of the immune system function normally and of the role of immune mechanisms in the prevention and pathogenesis of diseases.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; molecular genetics, developmental biology, repertoire and specificity of antigen-binding receptors of lymphocytes; and the degree of specialization of individual immunocompetent functional cells. Utilization of many modern techniques in the study of immune responses will be made, including production and use of monoclonal antibodies, cloning and long-term growth of lymphocyte lines; molecular genetic analysis of cells of the immune system; cell biological analysis of lymphocyte activation and differentiation; preparation of transgenic mice to analyze functions of immunologically important genes. Medical staff fellows will have the opportunity to participate in studies in

one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff

Cellular immunology; cellular and developmental biology of lymphocytes; regulation of the immune response—

Thomas M. Chused, M.D.

Richard Asofsky, M.D.

William E. Paul, M.D.

Ethan M. Shevach, M.D., and

Michail V. Sitkovsky, Ph.D.

Molecular genetics of lymphocytes; immunochemistry—

Ronald N. Germain, M.D., Ph.D.

John K. Inman, Ph.D.

Rose G. Mage, Ph.D., and

David Margulies, M.D., Ph.D.

Laboratory of Parasitic Diseases—

Franklin A. Neva, M.D.

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis on those affecting man. A variety of protozoan (malaria, trypanosomes, giardia, leishmania, amebae, and toxoplasma) and helminth (schistosomes, filaria, and strongloides) parasites are used for experimental work. Current studies include molecular and cell biology, biochemistry, immunologic mechanisms of antigenic recognition and parasite destruction, and host-parasite interactions *in vitro* and *in vivo*.

Increasing emphasis is being devoted to the immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis, and filariasis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite.

When appropriate, certain problems that can only be investigated in the field are studied in collaboration with institutions overseas. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients are seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, medical staff fellows can select their area of work and a preceptor. In addition, an organized program provides medical staff fellows with an exposure to clinical parasitology.

Research Areas and Senior Staff

Host-Parasite Relations—

A. W. Cheever, M.D.

Cell Biology and Immunology—

F. A. Sher, Ph.D.

Clinical Parasitology—

F. A. Neva, M.D.

T. E. Nash, M.D., and

E. A. Ottesen, M.D.

Malaria—

L. H. Miller, M.D.

Laboratory of Molecular Microbiology—

Malcolm A. Martin, M.D.

The Laboratory of Molecular Microbiology uses molecular biological techniques to study microorganisms and their capacity to produce disease in vertebrate hosts. Of prime importance is the biochemical characterization of viral and bacterial genomes and the detailed analyses of gene products regulating expression or giving rise to mature structural proteins.

A principal area of investigation has been the human immunodeficiency virus (HIV). Classical virological procedures are used for the detection, quantitation, and biological characterization of HIV isolates of diverse origin. Biochemical and molecular biological techniques such as nucleic acid hybridization, gene cloning, DNA sequencing, *in vitro* mutagenesis, and

transfection are used in combination with procedures such as immunoprecipitation or protein purification to study individual viral genes or potentially infectious proviral DNAs to assess structure/function relationships.

Programs involving DNA tumor viruses and murine retroviruses concentrate on those portions of the viral genome that encode proteins that initiate and/or maintain the transformed state. The roles of host cellular determinants that augment or diminish disease/oncogenesis are also investigated.

Senior Staff

Kuan-Teh Jeang, M.D., Ph.D.

Arifa Khan, Ph.D.

Christine Kozak, Ph.D.

Arnold Rabson, M.D.

Roy Repaske, Ph.D.

Jonathan Silver, M.D.

Sundaravajan Venkatesan, M.D.

Laboratory of Immunopathology

Herbert C. Morse III, M.D.

This laboratory conducts basic research on development of the immune system and abnormalities of development and function caused by virus infections and autoimmune diseases. Viruses under study include murine retroviruses and papovaviruses. Areas of current study include:

- Pathogenesis of retrovirus infections causing lymphomas and leukemias.
- Pathogenesis of retrovirus-induced immunodeficiency.
- Molecular genetic comparisons of retroviruses with different disease-inducing characteristics.
- Mechanisms in hematopoietic differentiation with emphasis on B cells.
- Immune resistance to tumors induced by papovaviruses.

Research projects for Medical Staff Fellows are chosen after discussions of possible topics with members of the laboratory. Training in virology, cellular immunology, tissue culture, flow cytometry and molecular biology is provided during the course of study. Results are discussed informally in research meetings of the laboratory members and informal talks with preceptors.

Research Areas and Senior Staff

Immunopathology—

Herbert C. Morse III, M.D.

Retroviral pathogenesis—

Janet W. Hartley, Ph.D., and

Herbert C. Morse III, M.D.

Molecular virology—

Sisir Chattopadhyay, Ph.D.

Papovaviruses—

Andrew M. Lewis, Jr., M.D.

Hematopoietic differentiation—

Kevin L. Holmes, Ph.D., and

Herbert C. Morse III, M.D.

Biological Resources Branch—

Scientists in the Biological Resources Branch are involved in research directed toward defining the components of the immune response and the molecular basis of their reactivities. The approaches used in these studies emphasize the development of specific serologic reagents, structural biochemistry, molecular biological techniques, and *in vitro* analyses of immune function. The branch maintains protein sequencing, peptide synthesis, and fluorescence-activated cell sorting (FACS) facilities.

Areas of active investigation include studies on T-lymphocyte antigen receptors and the major histocompatibility complex (MHC) class I and class II molecules that present antigens to these T cell receptors; factors regulating the expression of T cell antigen receptors and MHC molecules such as cytokines and their receptors as well as DNA-binding proteins; accessory molecules like CD4 and CD8 involved in the binding and activation of T-lymphocytes; and mechanisms of antigen processing for presentation to T-lymphocytes with particular emphasis on viral antigens. Additional studies focus on hematopoietic cell differentiation using neoplasms as model systems.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. Training in the areas of molecular biology, protein chemistry, immunochemistry, production of monoclonal

antibodies and anti-peptide sera and immunologic assays for cellular and humoral components of the immune response is provided during the course of investigation. In the course of study, appointees should gain a thorough understanding of the technical and conceptual aspects of immunology.

Research Areas and Senior Staff

Molecular Immunology—

John E. Coligan, Ph.D., and

W. Lee Maloy, Ph.D.

Hematopoietic Cell Differentiation—

Kevin Holmes, Ph.D.

Laboratory of Cellular and Molecular Immunology—

Ronald H. Schwartz, M.D., Ph.D.

This laboratory studies the biology of thymus-derived (T) lymphocytes at both the cellular and molecular levels. The training emphasis is centered on developing a cell biology problem in immunology and then moving one's understanding of this problem to the molecular level. Current problems under investigation include the mechanisms of immune response (Ir) gene control with particular emphasis on the role of Ia molecules in T cell activation; ontogeny of T cell antigen-specific receptor expression, with emphasis on the positive and negative selection events that shape the final T cell repertoire; and tolerance induction in T cell populations, with emphasis on the biochemical events that occur during the induction of a nonresponsive state in individual cells. Medical staff fellows will receive training in cellular immunology, immunogenetics, tissue culture, protein biochemistry and molecular biology. Techniques used include lymphocyte cloning, creation of radiation-induced bone marrow chimeras, monoclonal antibody production, peptide synthesis, protein isolation and *in situ* hybridization. Conceptual training consists of weekly journal clubs, data presentation sessions and research seminars, and summer tutorial courses in immunology on relevant topics such as MHC restriction and Ir gene control. Fellows will work under the direct supervision of the Chief of the laboratory or one of the senior staff.

Research Areas and Senior Staff

T Cell Activation and Ir Gene Control—

Ronald H. Schwartz, M.D., Ph.D.

T Cell Ontogeny—

B. J. Fowlkes, Ph.D.

T Cell Tolerance—

Polly Matzinger, Ph.D.

Rocky Mountain Laboratories

The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—

Bruce W. Chesebro, M.D.

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance, and elimination of persistent viral infections. Particular emphasis is placed on persistent viral infections involving cells of the hematopoietic and lymphoid systems and the central nervous system. The role of persistent infection in the development of autoimmune or immune complex disease is also being studied. Models examined include human AIDS retrovirus, murine, avian and equine retroviruses, rabies virus, Aleutian disease virus of mink, and the scrapie agent.

Research Areas and Senior Staff

Retroviruses—

Bruce Chesebro, M.D.

John Portis, M.D.

Leonard Evans, Ph.D.

Rabies—

Donald Lodmell, Ph.D.

Aleutian Disease Virus—

Marshall Bloom, M.D.

Scrapie—

Richard Race, D.V.M., and

Bruce Chesebro, M.D.

Acute Phase Serum Proteins—

John Coe, M.D.

Laboratory of Microbial Structure and Function—

John Swanson, M.D.

Pathogenic bacteria is studied in this laboratory to discover those components that influence the pathogens' interactions with animal or human hosts. Of primary interest are constituents that comprise the pathogens' surface facades and dictate the prokaryotes' styles of pathogenesis, virulence, and immunoreactivity. Extracellular pathogens such as gonococci and several obligate intracellular bacterial parasites (primarily chlamydiae and rickettsiae) receive major attention regarding the structural, functional, and immunochemical attributes of their outer membrane moieties. Genetic mechanisms involved in the expression and antigenic variation of these surface components are explored to amplify and complement their characterizations by biochemical and immunological parameters. Extensive use of animal models of infection provides insight into the relevance of findings gained at subcellular and molecular levels.

Research Areas and Staff—

Chlamydia—

Harlan Caldwell, Ph.D.

Gonococci—

John Swanson, M.D.

Laboratory of Pathobiology—

Claude F. Garon, Ph.D.

Members of this laboratory use modern methods of molecular biology in several medically important systems to characterize in molecular terms important features of the host-pathogen relationship. The Laboratory of Pathobiology consists of four sections which describe broad areas of interest. The Molecular Pathobiology Section is working on the molecular cloning and expression of genes relevant to the toxic components of *Bordetella pertussis*. The Arthropod-borne Diseases Section concentrates on two vector-borne spirochetes: *Borrelia hermsii*, an agent of relapsing fever, and *Borrelia burgdorferi*, the agent of Lyme disease. The Immunopathology Section is involved in studies on the immunopotentiating actions of *campylobacter* and bacterial protein toxins. The Pathobiology Section is responsible for research utilizing

modern methods of transmission and scanning electron microscopy, as well as other techniques, to define those structural alterations in either tissue or nucleic acids that are related to the pathological condition. An important by-product of these studies is the potential to identify and to exploit specific bacterial bioproducts for improved diagnostics and vaccines.

Research Areas and Senior Staff

Nucleic Acid Electron Microscopy—

Claude F. Garon, Ph.D.

Arthropod-borne Diseases—

Tom G. Schwan, Ph.D.

Warren J. Simpson, Ph.D.

Molecular Pathobiology—

Jerry M. Keith, Ph.D.

Immunopathology—

John J. Munoz, Ph.D.

Witold Cieplak, Ph.D.

Medical Entomology—

Willy Burgdorfer, Ph.D. (Emeritus)

National Institute on Deafness and Other Communication Disorders

Jay Moskowitz, Ph.D.
Acting Director

The National Institute on Deafness and Other Communication Disorders has one position available for a medical staff fellow. The appointment is for 2- or 3-years. The fellow will work under the guidance of one of the senior investigators in the speech and voice unit. For further information, write Christy Ludlow, Ph.D., National Institutes of Health, NIDCD, Building 10, Room 5N226, Bethesda, MD 20892.

Speech and Voice Unit

—Christy L. Ludlow, Ph.D.

This unit is concerned with the control of laryngeal and vocal tract structures for speech and voice production. Mechanisms for the normal generation of speech and voice, the pathophysiology of speech and voice disorders such as spasmodic dysphonia, stuttering and dysarthria and the development of new treatment approaches for these disorders are the major interests. Investigations involve careful clinical evaluation, physiological investigation and clinical trials examining the efficacy of new surgical and medical techniques. Physiological investigations include: electromyography of the laryngeal and speech musculature; lip, jaw and laryngeal movement transduction; air flow and air pressure transduction; and quantitative analysis of physiological responses in the larynx and vocal tract to alterations in sensory and motor stimuli. Treatment investigations involve the objective evaluation and analysis of the effects on voice, speech, the larynx and vocal tract pathophysiology of botulinum toxin injections, neuropharmacological manipulation and phonosurgery.

National Institute of Diabetes and Digestive and Kidney Diseases

Phillip Gordon, M.D.

Director

Jesse Roth, M.D.

Director of Intramural Research

James E. Balow, M.D.

Clinical Director

Appointments in Clinical Research

Each medical staff fellow is assigned to one of the Institute's clinical branches or sections, in which he or she carries out both clinical work and laboratory studies. The fellow is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The fellow is encouraged to choose his or her own problem for independent investigation, if facilities, technical advice, and supervision are available. In addition, the fellow provides professional care for research patients admitted to the service of the branch chief and assist in the outpatient department. There is considerable variation among the branches of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with respect to the proportion of the fellow's time required for patient care activities.

Medical staff fellows of the Clinical Endocrinology, Diabetes, Metabolic Disease, and Molecular, Cellular, and Nutritional Biology branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIDDK fellows may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new medical staff fellows each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the

areas of interest. Prospective applicants desiring more information should write to James E. Balow, M.D., Clinical Director, NIDDK, Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20892. Supplementary information sheets on each branch, together with selected bibliographic citations are available on request.

Appointments in Laboratory Research

NIDDK has four positions in laboratory research available each year for medical staff fellows. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research (in some cases, arrangements can be made for an additional year to satisfy specialty board requirements). During their stay here, fellows will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The medical staff fellow, approximately 1 year prior to beginning, will visit NIDDK to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing Jesse Roth, M.D., Director of Intramural Research, NIDDK, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIDDK programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Developing Programs

Programs in clinical and basic research are being developed in NIDDK in the following areas: nephrology, nutrition, and cystic fibrosis. For further information, contact Jesse Roth, M.D., or James E. Balow, M.D., Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment for studying the epidemiology of chronic diseases such as diabetes and arthritis among the Pima Indians of Arizona. In addition, clinical research opportunities in the causes, complications, and treatment of diabetes and in the relationships between lipoprotein metabolism, obesity and diabetes are available at the Clinical Diabetes and Nutrition Section in the Phoenix Indian Medical Center. Most candidates complete post-doctoral training before beginning this fellowship. Occasionally, candidates begin the fellowship after completion of an internship. Candidates interested in clinical research are encouraged to write to Clifton Bogardus, M.D., Clinical Diabetes and Nutrition Section, 4212 N. 16th Street, Phoenix, Arizona 85016. Those interested in epidemiology should write Peter H. Bennett, M.D., Epidemiology and Field Studies Branch, NIDDK, 1550 E. Indian School Road, Phoenix, Arizona 85014, for more detailed information.

Clinical Endocrinology Branch—

Jacob Robbins, M.D.

Jan Wolff, M.D., Ph.D., and

Vera Nikodem, Ph.D.

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid hormones. Laboratory research encompasses fundamental and applied protein chemistry, cell biology, and molecular biology. In addition to clinical rotation in the Interinstitute Endocrinology Training Program, the fellow is assigned to a senior scientist for the full 3-year appointment. Clinical studies focus on the management of thyroid neoplasms. Current laboratory research projects include: 1) the mechanism of thyroid transport into target cells utilizing cultured cell systems; 2) the interaction of thyroid hormones with lipoproteins and their role in intracellular targeting; 3) the interaction of the cytoskeleton, especially microtubules, with cell membrane function, and the regulation of microtubule polymerization; 4) the regulation of membrane-bound and soluble adenylate cyclase by hormones, calmodulin, bacterial toxins, etc.; 5) the molecular mechanism of thyroid hormone regulated gene expression utilizing *in vitro* and *in vivo* transcription systems, characterization and cloning

of transcription factors, and examining their interaction with DNA binding sites; 6) developmental, hormonally regulated and tissue specific expression and processing of the thyroid hormone receptor gene.

Molecular, Cellular and Nutritional Endocrinology Branch

Molecular Regulation and Neuroendocrinology Section—

Bruce D. Weintraub, M.D., and

Irwin M. Chaiken, Ph.D.

This section conducts basic and clinical investigations on the regulation of hypothalamic, pituitary, and placental polypeptide hormones. Current studies focus on the regulation of transcription, glycosylation, secretion and action of thyrotropin, gonadotropins, and vasopressin in various cell lines, animal models, and patients. A number of *in vivo* techniques are employed in both animals and patients, and a wide variety of *in vitro* techniques are applied from the areas of molecular and cell biology, neuroendocrinology, biochemistry, and hormone action. Clinical investigations are related to disorders of the hypothalamus, pituitary and thyroid, particularly involving thyrotropin-releasing hormone, thyrotropin, and thyroid hormone action.

Experimental Diabetes, Metabolism and Nutrition Section—

Samuel W. Cushman, Ph.D., and

Ian A. Simpson, Ph.D.

This section 1) investigates the structure, function and biosynthesis of integral membrane proteins involved in the hormonal regulation of carbohydrate and lipid metabolism, especially the receptors for insulin and insulin-like growth factor II, and the glucose transporter; 2) studies the molecular and cellular basis of hormone action, especially relating to the mechanism of insulin action and its counterregulation by catecholamines, other peptide hormones, and the glucocorticoids; and 3) examines the influence of altered metabolic and nutritional states on cellular function and its regulation by hormones, especially those states associated with perturbed

insulin action such as diabetes, obesity, and altered dietary carbohydrate and fat intake.

Growth and Development Section—

Matthew M. Rechler, M.D.

The mission of this section is to understand the mechanisms by which hormonal, nutritional, and cellular factors interact to regulate cell growth in different physiological states (i.e., fetal/embryonic development, postnatal growth, wound repair, neural cell growth and maintenance), and how these controlled processes become deranged in pathological states involving excessive or inadequate cell growth (e.g., intrauterine growth retardation, dwarfism, neoplasia, atherosclerosis, diabetic retinopathy). The biosynthesis and action of polypeptide hormones/growth factors and their regulation will be studied in appropriate model systems (e.g., cell cultures established from human subjects and animals), using state-of-the-art techniques of molecular and cell biology. Special emphasis will be given to interactions between different cell types and their products, to regulation of tissue responsiveness to growth factors, and to alternative expression of growth factor genes resulting in novel peptides with biological functions not directly related to cell growth.

Clinical Hematology Branch—

N. Raphael Shulman, M.D.

Laboratory work concerns problems in the fields of immunohematology, platelet physiology and metabolism, and blood coagulation. Current interests include mechanisms of immune cellular injury involving drug, allo-, and auto-antibodies, correlation of platelet metabolism and membrane reactions with function, and interrelationships between cellular and humoral factors in hemostasis. Clinical work involves patients with immunologic and hemorrhagic disorders relevant to laboratory studies.

Diabetes Branch—

Jesse Roth, M.D.

Derek LeRoith, M.D., Ph.D.

Simeon I. Taylor, M.D., Ph.D.

Flora de Pablo, M.D., Ph.D.

Phillip Gorden, M.D., and

Richard C. Eastman, M.D.

Members of the Diabetes Branch study peptide hormones and growth factors, particularly insulin and the insulin-like growth factors (IGFs) and their receptors using clinical, biochemical, developmental, cell biological and molecular biological approaches. Current projects are focused on:

- the role of receptors in disease states; receptor antibodies; genetic disorders of glucose metabolism; characterization of receptor components including posttranslational modifications; receptors on circulating cells and cells in culture studied by biochemical and morphological methods.
- the molecular basis of insulin resistance with special attention to the use of recombinant DNA technology to identify mutations of the insulin receptor gene.
- the molecular basis of insulin action including identification of substrates for phosphorylation by the insulin receptor and IGF-I-receptor-associated protein kinases.
- insulin receptors and insulin action in the central nervous system including mapping of receptors by autoradiographic techniques and metabolic and other effects of insulin in the CNS.
- the role of insulin and the IGFs in embryonic development including ontogeny of their mRNAs and characterization of insulin and IGF receptors in embryonic tissues.
- evolutionary approach to analyze the presence and action of insulin-like and other hormone-like peptides including cloning of these peptides cDNAs for non-mammalian species and purification of the equivalent peptides in *Saccharomyces Cerevisiae* and *E. coli*.

Advances in the laboratory are rapidly applied to appropriate problems in human disease states.

Digestive Diseases Branch—

- Section on Gastroenterology—
Jerry D. Gardner, M.D., and
Robert T. Jensen, M.D.

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunologic processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Liver Diseases Section—
E. Anthony Jones, M.D., and
Jay H. Hoofnagle, M.D.

Programs are concerned with research into hepatic physiology, immunology, and disease. Laboratory research projects include studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and chronic viral hepatitis, investigations of the significance of various viral antigens and antibodies in chronic type B hepatitis; characterization of the molecular biology of chronic type B hepatitis; and evaluation of pathogenetic mechanisms that contribute to hepatic encephalopathy in animal models of fulminant hepatic failure and chronic liver failure. Clinical investigations include trials of interferon and other antiviral agents in the treatment of chronic type B hepatitis, chronic delta hepatitis and chronic non-A, non-B hepatitis, and trials of immunosuppressive therapy for primary biliary cirrhosis.

Genetics and Biochemistry Branch—

R. Daniel Camerini-Otero, M.D., Ph.D.
April Robbins, Ph.D.
Richard Proia, Ph.D., and
Eric Ackerman, Ph.D.

The branch conducts studies in clinical, biochemical, developmental and molecular genetics. The range of current projects covers a wide field from the very basic (e.g., mechanisms of genetic recombination and gene conversion in mammalian cells, DNA-mediated gene transfer, the regulation of gene expression, the molecular biology of early development in *Xenopus laevis*, biosynthesis and transport of lysosomal proteins, the molecular mechanisms of endocytosis and the

biochemical and molecular bases of human genetic disorders) to the more applied (development of new diagnostic tests and carrier detection for a number of human genetic diseases and the development of new techniques for gene purification and transfer).

Medical staff fellows seeking training in medical genetics may apply to this branch and participate in the NIH Interinstitute Medical Genetics Program (see page 10). The program fulfills all the requirements of the American Board of Medical Genetics and completion of a genetics fellowship in this program leads to board eligibility in this subspecialty. Candidates must have training in a medical specialty such as internal medicine or pediatrics.

Laboratory of Chemical Biology—

Alan N. Schechter, M.D.

The clinical focus of this section is on the molecular pathophysiology of the hemoglobinopathies and other genetic diseases. Basic studies are concentrated on using molecular genetic techniques to examine normal and abnormal erythrocytes and human erythroid cells. Protocols to alter gene expression in patients with hemoglobinopathies, as well as several clinical protocols, designed to develop non-invasive methods, including laser-Doppler velocimetry, NMR and other imaging modalities, to assess the severity of sickle cell anemia and to follow the results of therapy are underway. The section participates in the NIH Interinstitute Clinical Genetics Program. (For non-clinical studies see Basic Research Laboratory listing.)

Metabolic Diseases Branch—

Gerald D. Aurbach, M.D.

Stephen J. Marx, M.D.

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, calciferol and parathyroid hormone. A number of ligands and factors controlling growth, secretion, and differentiation in parathyroid, bone and other tissues are under study using cell biology techniques.

The clinical program involves studies of patients with disorders of mineral metabolism. These include patients with hereditary resistance to parathyroid hormone or to calciferols. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is used for *in vitro* studies on control of endocrine cell growth and hormone secretion.

Molecular Pathophysiology Branch—

Allen M. Spiegel, M.D.

A family of guanine nucleotide binding proteins (G proteins) transduces signals across membranes by coupling receptors to effector enzymes. Distinct G proteins couple: 1) receptors for hormones and neurotransmitters that stimulate or inhibit cAMP formation; 2) rhodopsin, a photon receptor, to a cGMP phosphodiesterase; and 3) receptors for agonists that stimulate phosphatidylinositol turnover. The Molecular Pathophysiology Branch studies the structure and function of G proteins. G proteins that have been purified and used for the production of antibodies have proved useful for studies of G protein structure, for immunocytochemical studies, for regional localization of G protein in brain, and for quantitation of G proteins as a function of cell differentiation. The Branch studies states of altered target cell responsiveness for possible quantitative or qualitative changes in G proteins. Thus, a human genetic disorder characterized by generalized hormone resistance has been shown to result from a deficiency in the G protein linked to adenylate cyclase stimulation. The Branch also searches for novel G proteins involved in membrane transduction. Such a protein has been identified in human neutrophils. In addition, cDNA probes are employed to study alterations in G protein structure and synthesis.

Phoenix Clinical Research Section—

Clifton Bogardus, M.D.

Barbara V. Howard, Ph.D., and

Peter H. Bennett, M.B.

This section is currently involved in studies of diseases particularly prevalent among southwestern American Indians.

One of the major areas under investigation is diabetes mellitus in the Pima Indian population. This group has the world's highest reported prevalence of type II (noninsulin dependent) diabetes. The geographical proximity of this unique population to the Phoenix area provides an excellent opportunity for insight into the causes and complications of type II diabetes. A problem closely related to the diabetes in this group is that of obesity. These areas are under intensive scientific investigation in both the 21-bed clinical research unit and the basic science research laboratory which are co-located within the Indian Health Service Referral Hospital, Phoenix, Arizona.

Clinical studies currently in progress include whole-body insulin resistance, nutrition-induced alterations in metabolism, lipid and lipoprotein metabolism, and dietary and exercise therapy in the treatment of diabetic patients, and studies of energy expenditure using a human respiratory chamber. The laboratory research is centered around insulin-mediated glucose metabolism in muscle from diabetic and nondiabetic donors, lipoprotein metabolism, as well as a variety of studies supporting the clinical investigations.

Close collaboration with the Epidemiology and Field Studies Section allows investigation into the prevalence of not only diabetes and obesity, but also cardiovascular disease, gall bladder disease, lipid and lipoprotein abnormalities, and rheumatoid arthritis in the Pima Indians.

Southwestern Field Studies Section

William C. Knowler, M.D.

David J. Pettitt, M.D., and

Peter H. Bennett, M.B.

This section, located in Phoenix, Arizona, conducts research in the etiology of diabetes and its associated risk factors, genetic determinants, vascular complications, and natural history in the 20-year longitudinal study among the Pima Indians of Arizona. Staff fellows participate in data collection and monitoring, and in analysis and publication of results from this study. They may also engage in activities relating to the design, monitoring or analysis of clinical trials in the field of diabetes and its complications. The section has additional activities in the epidemiology of arthritis, and renal, metabolic and digestive diseases, such as gallbladder disease. Staff of the section

may also collaborate with the Phoenix Clinical Research Section, NIDDK, on in-patient metabolic studies related to diabetes, obesity, and lipoprotein metabolism.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—

Herbert Tabor, M.D.

Simon Black, Ph.D.

Anthony Furano, M.D.

Victor Ginsburg, Ph.D.

Leonard D. Kohn, M.D.

Nancy Nossal, Ph.D., and

Reed B. Wickner, M.D.

The work of this laboratory includes a large variety of biochemical, genetic, and molecular biological investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, and yeast and *Escherichia coli* genetics. Studies are also carried out on developmental biology and genomic structure and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these members to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance.

A third section is concerned with the biology and immunology of the complex carbohydrates of animal cell surfaces.

A fourth section is studying the genetic control of replication of a double-stranded RNA virus of yeast and other problems in the genetics of simple eukaryotes.

Laboratory of Biochemistry and Metabolism—

G. Gilbert Ashwell, M.D.

Enrico Cabib, Ph.D.

Evelyn Grollman, M.D.

John Hanoner, Ph.D.

Lothar Hennighausen, Ph.D.

William B. Jakoby, Ph.D.

Leonard D. Kohn, M.D.

Peter McPhie, Ph.D.

Rachel Myerowitz, Ph.D.

Adrian Parsegian, Ph.D.

April Robbins, Ph.D.

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; studies on the mechanism of receptor-mediated endocytosis and glycoprotein-membrane sorting in eukaryotes using biochemical methods as well as those of somatic cell mutation; study of the cluster of enzymatic activities, classified as enzymes of detoxification, that function in the conjugation of foreign compounds in mammals; and a study at the molecular biology level of thyroid function. In addition to the above general areas, specific projects of individual investigators include a study of the enzymes involved in carbohydrate metabolism; the molecular basis of Tay-Sachs disease; regulation of gene expression by nuclear protein transcription factors; thermodynamic and kinetic studies on enzymatic and protein-folding mechanisms; the biophysics of hydration of macromolecules and of membrane-membrane interaction.

Laboratory of Bioorganic Chemistry—

John W. Daly, Ph.D.

Donald M. Jerina, Ph.D.

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active

substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of actions or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathologic function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, central stimulants, depressants, local anesthetics, other therapeutic agents, toxins, carcinogens, mutagens, and mechanism-based enzyme inhibitors.

Laboratory of Chemical Biology—

Alan N. Schechter, M.D.

Hiroshi Taniuchi, M.D., Ph.D.

Research in this laboratory is focused on the control of gene expression, on the folding of proteins, and on the forces stabilizing macromolecules. Dr. Schechter and his group are studying the control of hemoglobin synthesis, using molecular genetic techniques in cultured human erythroid cells. The work includes studies of the *cis* and *trans*-acting factors that affect transcription and translation. In addition, biophysical methods, especially NMR spectroscopy, are being used to study molecular interactions inside erythrocytes, including the polymerization of sickle hemoglobin. Dr. Taniuchi and his colleagues are studying the folding and dynamics of proteins, using cytochrome *c* as a model, with a variety of chemical and physical techniques, including peptide synthesis and NMR.

Laboratory of Chemical Physics—

Edwin D. Becker, Ph.D.

Elliot Charney, Ph.D., and

William A. Eaton, M.D., Ph.D.

William A. Hagins, M.D., Ph.D., and

Ira W. Levin, Ph.D.

Research in this laboratory is characterized by the application of modern physical techniques to the study of a wide range of biological problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S, development of new nuclear magnetic resonance methods for determination of the structure of large molecules in solution, study of the association of mononucleotides and of the conformational behavior of polynucleotides, investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes, analysis of excited electronic states of small molecules in the vapor phase and in molecular beams, development of methods for asymmetric synthesis, study of the structural characteristics of model membrane systems, the structure and dynamic behavior of nucleic acids and proteins, and the dynamics of ligand binding and structural changes in hemoglobin. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism, ultraviolet and visible microspectrophotometry, and time-resolved absorption spectroscopy with nanosecond lasers.

Laboratory of Chemistry—

Bernhard Witkop, Ph.D., Sc.D.

Louis A. Cohen, Ph.D.

Cornelius P. J. Glaudemans, Ph.D., and

Kenner C. Rice, Ph.D.

In the oldest laboratory of the Institute (founded June 20, 1905), chemistry is represented in its broadest context in three independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, immunochemistry, novel toxins, metabolism, antiviral agents, interferon, and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder

cancer, effects of novel colchicine derivatives on microtubules, separation of addictive from analgesic properties in new synthetic morphine substitutes, characterization of sodium channels in electrogenic membranes by a frog toxin, the acetylcholine receptor, development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes, hypoxic cell sensitizers, cytotoxic agents selective for cancer cells, the interaction between antigens and monoclonal antibodies, recombinant hybrid immunoglobulins and the detailed structure of fungal antigens.

Laboratory of Cell Biology and Genetics—

Harvey B. Pollard, M.D., Ph.D.

Eduardo Rojas, Ph.D.

Illani Atwater, Ph.D.

Richard Ornberg, Ph.D., and

A. Lee Burns, Ph.D.

The laboratory carries out basic studies and collaborative clinical studies relating to mechanisms regulating secretion of hormones and transmitters from endocrine nerve and endothelial cells. This work includes electrophysiological studies involving microelectrodes and patch techniques; electron microscopy using fast freezing, freeze etch, and elemental imaging methods; molecular biology involving construction of cDNA libraries cloning and sequencing; and basic cell biology techniques involving optical microscopy, monoclonal and polyclonal antibody production, and protein purification.

Laboratory of Molecular Biology—

Martin Gellert, Ph.D.

Jun-ichi Tomizawa, Ph.D.

Gary Felsenfeld, Ph.D.

David R. Davies, Ph.D.

Robert Martin, Ph.D.

H. Todd Miles, Ph.D.

Terrell Hill, Ph.D., and

Kiyoshi Mizuuchi, Ph.D.

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the

molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, and studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters). Other investigations are concerned with the structure and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Cellular and Developmental Biology—

Robert T. Simpson, M.D., Ph.D.

Jurrien Dean, M.D.

Constantine Londos, D.D.S., Ph.D.

Robert O. Scow., M.D.

Ann Dean, Ph.D.

Alan Kimmel, Ph.D.

Bernard T. Kaufman, Ph.D.

Robert W. Hartley, Ph.D.

This laboratory studies the regulation of gene expression. Studies are carried out with a wide spectrum of experimental systems, simple unicellular organisms such as yeast and *Dictyostelium*, sea urchins, model systems using cells in tissue culture and mice. Emphasis is on the understanding of both DNA motifs that are important in gene regulation and chromatin structure of the regulated gene. Two groups study hormonal effects on adipocytes and lipid transport mechanisms. Several proteins are studied with a view to elucidating structure and function relationships. These include a prokaryotic ribonuclease and its inhibitor and dihydrofolate reductase.

Mathematical Research Branch—

John Rinzel, Ph.D.

The branch conducts research on the mathematical and theoretical aspects of biological systems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis

and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level, electrotonus in neuronal dendritic systems, excitability and auto-rhythmicity in neuroelectric signaling, bifurcation, and stability studies of nerve conduction and diffusion-reaction systems, nonlinear chemical/biochemical oscillations, analysis of nucleic and amino acid sequences, and mathematical modeling of renal function.

Duane Alexander, M.D.

Director

Arthur S. Levine, M.D.

Scientific Director (Director, Intramural Research)

D. Lynn Loriaux, M.D., Ph.D.

Clinical Director

The Intramural Research Program is concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. In addition to four major clinical research and training programs in the areas of genetics and endocrinology, a diversity of developmental models are under study in twelve fundamental research laboratories, drawing upon observations in bacteria, *Drosophila*, yeasts, viruses, molluscs, frogs, rodents, and subhuman primates. Disciplines employed in these studies include biochemistry, virology, molecular biology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics, mathematical and theoretical biology, reproductive physiology and developmental psychology.

Each medical staff fellow will devote time to research in the laboratory under the supervision of a senior preceptor. Each is expected to engage in appropriate course work in the basic and/or medical sciences as well as tutorial seminars, and to take an active part in the journal club, lecture series, and other laboratory exercises.

All appointments as medical staff fellows are for a minimum of 2 years. Most fellows elect to remain for 3 full years and are offered this opportunity. For highly qualified fellows, additional years of training are possible.

The Intramural Research Program's twelve branches and laboratories are each under the direction of a branch or laboratory chief. Fellowship positions are usually available in all of these areas. The fellows have an exceptional opportunity to become independent scientists in a field of their interest, and to prepare themselves for a career in academic medicine and research.

Prospective applicants wishing further information should write to Arthur S. Levine, M.D., Scientific Director, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892. In writing, please be specific as to your interests and the information you require.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research.

Medical staff fellows will be responsible, under the guidance of senior investigators on the NICHD staff, for the primary medical care of research patients during the first year of their service. During this time, they will serve in the medical units that are associated with the clinically oriented branches of the Institute and assist in the work of the service with inpatient care, consultation and in the outpatient department. The clinical period offers exposure to rich case material and to highly sophisticated approaches to clinical investigation.

The fellow devotes the subsequent time to laboratory research under direction of a senior preceptor in any one of the twelve Institute laboratories. The choice of laboratory is made during the fellow's first 6 months at NIH. No clinical responsibilities are required during the second or additional years for fellows who have chosen nonclinical laboratories.

The NICHD selects eight medical staff fellows each year who participate in one of the four approved clinical subspecialty training programs sponsored by this Institute: adult endocrinology, pediatric endocrinology, reproductive endocrinology, and medical genetics.

Fellows in adult endocrinology apply to the Developmental Endocrinology Branch and participate in the NIH Joint (inter-institute) Endocrinology Fellowship Program which leads to board certification by the American Board of Internal Medicine in the subspecialty of endocrinology and metabolism (see page 8). Applicants must be board eligible in the specialty of internal medicine prior to the initiation of the fellowship. The first year of the fellowship is primarily clinical. Further years are devoted to a research project which may be carried out in any of the twelve branches or laboratories of the NICHD.

Applicants for the pediatric endocrinology fellowship also apply to the Developmental Endocrinology Branch and must have completed PL-3 level training prior to the initiation of the fellowship. The first year is primarily clinical, with pediatric patient care responsibilities in the three endocrinology units associated with the NIH Joint Endocrinology Fellowship Program. The further years are spent in any one of the

branches or laboratories of the NICHD. This fellowship leads to board certification by the American Board of Pediatrics in the subspecialty of pediatric endocrinology.

Applicants for the reproductive endocrinology fellowship apply to the Office of the Scientific Director and must have completed an accredited residency in obstetrics and gynecology prior to the first fellowship year. The fellowship is a cooperative program utilizing the combined clinical facilities of the NIH, the National Naval Medical Center, and the Walter Reed Army Medical Center. The first year is entirely clinical, 3-6 months being spent on the combined endocrine services of the NIH, and 6-9 months in the infertility clinics of the two Service hospitals. The following years of the fellowship are spent in a research program that may be undertaken in any of the branches or laboratories of the NICHD. This program is recognized by the American Board of Obstetrics and Gynecology and leads to certification in the subspecialty of reproductive endocrinology.

Fellows in medical genetics apply to the Human Genetics Branch and participate in the NIH Interinstitute Medical Genetics program (see page 10). The program fulfills all of the requirements proposed by the American Board of Medical Genetics and leads to board certification in this subspecialty. Candidates may be pediatricians or internists, and occasionally represent other medical specialties such as neurology and obstetrics. As with the other NICHD clinical specialty programs, the first year of the fellowship is primarily clinical, with patient care responsibilities on the research wards of the NIH, Johns Hopkins, and Children's Hospital Genetics Clinics. The further years are spent in a research program in any NICHD laboratory or branch of the fellow's choice.

Applicants for all four of these programs are considered 1 or 2 years in advance of the proposed starting date. Application forms may be obtained from the NIH Medical Staff Fellowship Office, Building 10, Room 1C125, National Institutes of Health, Bethesda, MD 20892.

Appointments in Laboratory Research

Appointments are available which are designed to give highly qualified physicians an opportunity to do basic research in any area of the Institute under the direct supervision of a senior preceptor. Usually physicians enter the appointment after

completing internship and at least 1 year of residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises. Fellows with this appointment work exclusively with the branch or laboratory in which they are accepted, and make this choice at the time of initial application.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate School Foundation for Advanced Education in the Sciences, Inc. and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See page 296.)

Medical Staff Fellows in Pharmacology (PRAT)

Several of the NICHD laboratories and branches participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in areas relevant to pharmacology research. Candidates already trained in pharmacology may choose any NICHD senior scientist as a preceptor. For more information about the PRAT program, see page 177.

Clinical Research Branches

Developmental Endocrinology Branch—

D. Lynn Loriaux, M.D., Ph.D.

The endocrine concomitants of normal and abnormal human growth, development, and differentiation are examined in this branch, with studies in patients as well as animal models. Specific areas of clinical investigation include the mechanisms underlying the initiation of puberty; the regulatory physiology and biochemistry of the glycoprotein hormones; the roles of sex steroid hormones, growth hormones, and other growth factors in bone growth, and the physiology and biochemistry of the action of hypothalamic releasing hormones. Clinical research on male and female reproductive disorders is also a major interest of this branch.

- **Section on Steroid Hormones—**

D. Lynn Loriaux, M.D., Ph.D.

The mechanism of action of the steroid hormones is under investigation, including studies of the clinical disorders of masculinization, feminization, and glucocorticoid deficiency or excess. Patients with polycystic ovarian disease, gynecomastia,

polyendocrine deficiency, and Cushing's syndrome play an important role in the clinical research. Two syndromes of resistance to steroid hormone action, testicular feminization and cortisol resistance, are under intensive study.

- Section on Developmental Endocrinology—
Gordon B. Cutler, Jr., M.D.

This section studies the physiology and molecular endocrinology of normal growth and development. The neuroendocrine control of hypothalamic-pituitary-adrenal function and its role in metabolic and immune regulation are under investigation. Through improved basic knowledge of normal and pathologic mechanisms, the section seeks to improve the diagnosis and treatment of precocious and delayed puberty, congenital adrenal hyperplasia, Turner syndrome, growth hormone-deficient and non-growth hormone-deficient short stature, hirsutism and virilization, and Cushing's syndrome.

- Section on Medical Endocrinology—
Bruce C. Nisula, M.D.

The glycoprotein hormones, TSH, LH, FSH, and hCG, are the subjects of both clinical and basic research studies, and understanding the physiology of regulation of TSH, LH, and FSH secretion by the pituitary is a major goal. The development of new diagnostic procedures involving the glycoprotein hormones and evaluation of their clinical applications is emphasized. Clinical disorders of thyroid function and conditions characterized by abnormal glycoprotein hormone secretion are studied to elucidate the role of molecular heterogeneity in these situations. The regulation of thyroid function through the TSH receptor-adenylate cyclase system is of particular interest.

- Unit on Clinical Neuroendocrinology—
George P. Chrousos, M.D.

This group studies the regulation of hypothalamic-pituitary-adrenal function and its role in stress, metabolism, reproduction and immune regulation. By studying normal and pathologic mechanisms, the unit seeks to understand the pathogenesis of, and devise new therapies for, conditions associated with disorders of this axis. These include Cushing's syndrome, cortisol resistance, adrenal insufficiency, depression, anorexia nervosa and congenital adrenal hyperplasia. The role of corticotropin releasing hormone and glucocorticoids in

physiologic states such as exercise, puberty, the menstrual cycle, and pregnancy is also intensively studied.

- Unit on Reproductive Endocrinology—

George R. Merriam, M.D.

This group studies the regulation of reproduction and its disorders in normal subjects, patients, animals, and *in vitro* models. In clinical investigations, the aim is to understand the mechanisms underlying hypothalamic amenorrhea and hypogonadism, premature ovarian failure, polycystic ovary syndrome, luteal phase disorders, and infertility, and to develop new methods of treatment. Laboratory projects are focused on the neuroendocrine control of pituitary-gonadal function, the regulation of episodic hormone secretion, seasonal breeding, autoimmune gonadal disease, and the role of growth hormone and growth factors in reproduction.

Human Genetics Branch—

William A. Gahl, M.D., Ph.D. (Acting)

The Human Genetics Branch's interests range from studies on the etiology, diagnosis, and treatment of genetic and developmental disorders of young people to very basic studies on eukaryotic gene expression utilizing recombinant DNA methodology. There is a broad attempt to apply "genetic engineering" techniques to therapeutic strategies. The intent of the Branch's clinical fellowship program is to provide wide exposure to the field of human genetics, including clinical care, clinical research, and basic studies. Current research projects concern genetic disorders of lipid and carbohydrate metabolism, the mucopolysaccharidoses, heritable disorders of bone and connective tissue (with special emphasis on osteogenesis imperfecta), lysosomal storage diseases (e.g., cystinosis), temperature-sensitive models of cellular differentiation, the genetics of alcohol-related syndromes.

- Section on Human Biochemical Genetics—

William A. Gahl, M.D., Ph.D.

Clinical and laboratory methods are used to identify the biochemical etiology of genetic diseases such as cystinosis, Lowe syndrome, and undefined lysosomal storage disorders. Current topics include glycosaminoglycan synthesis and sulfation, and intracellular copper metabolism. New methods of prenatal and heterozygote detection are pursued, as is

treatment. Basic research involves study of the lysosomal transport of small molecules, including cystine, sialic acid, and tyrosine. Biochemical and molecular biological techniques are employed to isolate and characterize the integral membrane proteins responsible for this carrier-mediated transport.

- Section on Developmental Genetics—

Anil B. Mukherjee, M.D., Ph.D.

This section emphasizes biochemical, cellular, molecular biological, and immunological studies on early mammalian development. Special emphasis is given to the study of a steroid dependent, immunosuppressive protein, uteroglobin, lipocortins, and pp¹⁴ associated peptides which may have an important role in human reproduction. Additionally, basic and clinical investigations are conducted to understand the etiology of fetal alcohol syndrome and other alcohol-related disorders that may have a genetic component. Techniques utilized include tissue culture, protein chemistry and recombinant DNA methodology (including the expression of recombinant proteins in *E. coli* and site-directed mutagenesis).

- Section on Cellular Differentiation—

Janice Chou, Ph.D.

This section pursues studies on the molecular mechanisms responsible for eukaryotic gene expression during normal and abnormal differentiation processes. Temperature-sensitive liver and placental cell lines that retain differentiated tissue-specific functions are the primary experimental models. Current areas of research include developmental and hormonal regulation of liver-specific gene expression, with specific emphasis on the α -fetoprotein gene, the organization and expression of the pregnancy-specific β_1 -glycoprotein gene, a new member of the carcinoembryonic antigen gene family, and the organization and expression of the human alkaline phosphatase gene. Techniques utilized include recombinant DNA methodology, protein chemistry, tissue culture, and *in situ* hybridization methodology.

- Unit on Connective Tissue Disorders—

Joan Marini, M.D., Ph.D.

This unit studies the molecular biology of heritable disorders of connective tissue. There is an emphasis on osteogenesis imperfecta (OI) and the Ehlers-Danlos Syndrome, focusing on

the identification of disease-producing mutations, prenatal diagnosis and genetic patterns. Current studies involve the genes for Type I and Type III collagen. Techniques utilized include RNA/RNA hybrid analysis, DNA recombinant technology, the polymerase chain reaction and protein biochemistry. Clinical research projects are concerned with the basis of growth deficiency in OI.

- Section on Genetic Disorders of Drug Metabolism—
Ida S. Owens, Ph.D.

Investigations are directed toward Phase II drug metabolism, i.e., conjugation reactions in which enzymes (UDP glucuronosyltransferases) use as substrates bilirubin, endogenous steroids, or oxygenated drugs, carcinogens and other environmental pollutants. Mechanisms of gene expression and enzyme induction are explored via the use of immunochemical and recombinant DNA techniques, inbred strains of mice, normal and mutant cells in culture, and expression vectors.

Laboratory of Comparative Ethology

Stephen J. Suomi, Ph.D.

Research in this laboratory is focused on the development of behavior in humans, primates, and other animal models. The interactions of genetic and environmental factors are explored, using a comparative mammalian approach, so as to determine the origins and evolution of various behavioral phenotypes. Experimental results in animals are correlated with the results of longitudinal studies in human infants and families. Hypotheses concerning behavior in the animal models are correlated with results obtained by physiological and molecular neuroscience techniques.

- Section on Comparative Behavioral Genetics—
Stephen J. Suomi, Ph.D.

This section studies genetic and environmental interactions through comparative ontogenic study of rhesus monkeys and other animals (living under semi-natural conditions). The neuroanatomical, electrophysiological, and biochemical concomitants of various behavioral phenotypes are determined, and these phenotypes are tracked developmentally from birth through senescence. Monkeys bred to yield specific behaviors under stress (e.g., “laid back” or “uptight”) are used extensively in these longitudinal investigations.

- Section on Brain, Behavior and Communication—
David Symmes, Ph.D.

The focus of interest is on vocal communication, learning, and play among subhuman primates, and the relationship of these behaviors to those of humans. Study of monkeys living in social structures and within naturalistic habitats is an important aspect of research on vocal communication. The section also utilizes neurophysiological and neuropharmacological techniques to study coding of natural sounds in the CNS, and to elucidate the mechanisms of vocal production.

- Section of Child and Family Research—
Marc H. Bornstein, Ph.D.

This section investigates early development of human behavior and personality. These studies are undertaken within the context of family and cultural structures. Factors in the home that influence cognitive and social development are explored, such as interactive patterns between parents and infants, maternal employment, age and parenthood status.

- Section on Social and Emotional Development—
Michael E. Lamb, Ph.D.

Research in this section is focused on the factors affecting psychosocial and emotional adaptation in infancy, childhood, and adolescence in a variety of cultural and social contexts. Current research projects are designed to explore: the effects of out-of-home and home care experiences on the development of Swedish youth; the nature and effects of domestic violence; the correlates, antecedents, and consequences of adolescent pregnancy and parenthood; the antecedents of contrasting temperamental styles (“inhibited” and “uninhibited”); and the child care practices and belief of West Africans, West Germans, and North Americans.

- Unit on Neuroethology—
John Newman, Ph.D.

This unit studies the anatomy, chemistry and physiology of primate brain networks involved in the production of vocalizations, and examines the genetic basis for differences in characteristic vocalizations across individuals, populations, and closely related species of nonhuman primates. The pharmacology of vocal behavior is investigated in primate models of separation

anxiety and panic attack disorders. The acoustical characteristics of human crying are examined for diagnostic correlates with developmental disorders.

Basic Research Laboratories

Laboratories of the Scientific Director—

- Section on Viruses and Cellular Biology—
Arthur S. Levine, M.D.

DNA viruses (e.g., SV40 and adenoviruses) are used as model systems to understand mechanisms of mammalian growth regulation and cellular responses to mutagenic agents. Shuttle vectors based on viral genomic sequences are utilized in studies (*in vivo* and *in vitro*) on the molecular mechanisms of eukaryotic DNA replication, repair and mutagenesis. Factors involved in the control of the onset of DNA replication in the cell cycle, and in the control of the cellular stress response, are being investigated. The techniques of molecular biology (including DNA sequencing), biochemistry, tissue culture, virology, and immunology are employed.

- Section on Growth Factors—
Gordon Guroff, Ph.D.

This section focuses on the biochemical and physiological actions of nerve growth factor, a peptide required for the development of sympathetic and sensory neurons and portions of the central nervous system as well. Systems studied include the PC12 cell, a clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. Phosphorylative events and changes in gene transcription which may underlie differentiation are studied to define the exact molecular mechanism by which such peptide factors act.

Laboratory of Developmental Neurobiology—

Phillip G. Nelson, M.D., Ph.D.

The neurobiologic mechanisms relevant to development of the nervous system are investigated with emphasis on studies at the cellular membrane and molecular levels. The basis for short- and long-term interaction between nerve cells is studied electrophysiologically and biochemically. Combined molecular and morphological methods are used in the analysis of experimental modifications of brain function and gene expression.

- Section on Neurobiology—

Phillip G. Nelson, M.D., Ph.D.

Tissue-cultured neural and muscle tissue are studied, using intracellular electrophysiologic techniques and correlative light and electron microscopic morphologic methods. Neuropharmacological studies of pre- and post-synaptic receptors involve voltage-clamp and patch-electrode techniques. Studies of cholinergic function and neurodifferentiation employ molecular genetic, biochemical, and monoclonal antibody methods. Long-term interactions between nerve and muscle, and the influence of electrical activity on neural development, are of particular interest. Molecular biologic techniques are used to study gene expression during nervous system development.

- Section on Neuroendocrinology—

David C. Klein, Ph.D.

Investigations focus on the molecular mechanisms through which neurotransmitters regulate gene expression. Cultured pinealocytes are the primary experimental model. Current areas of study include the adrenergic control of pineal cyclic AMP and cyclic GMP, and the role of membrane protein phosphorylation in transsynaptic signal transduction. Recombinant DNA techniques are used to study the regulation of enzymes involved in the conversion of tryptophan to melatonin.

- Unit on Molecular Neurobiology—

Andres Buonanno, Ph.D.

This group aims to identify the genes coding for L-glutamate receptors (GR) and nicotinic acetylcholine receptors (nAChR), and to study how their expression is regulated both during development and by neurally induced electrical activity. One project uses recombinant DNA methodology, in conjunction with voltage-clamp recording, to identify cDNAs coding for GRs expressed in injected *Xenopus* oocytes. The cDNAs will be utilized to deduce the amino acid sequence of the subunits, to study the regional expression of the genes during development, and to analyze the effects of neural activity on the transcriptional modulation of receptor genes. Another project focuses on the identification of nuclear factors and DNA enhancers which interact to regulate the expression of muscle nAChRs during development and by electrical activity. Understanding at the molecular level how presynaptic neurons

modify the gene expression of target cells may reveal general mechanisms underlying synaptic plasticity.

- Unit on Cell Biology—

Elaine Neale, Ph.D.

This unit approaches basic questions of developmental neuroscience utilizing interdisciplinary methods, with emphasis on the correlates of structure and function. Studies include the role of interacting cell systems, endogenous trophic factors, and electrical activity on the ontogeny and function of the nervous system.

- Unit on Neurochemistry—

Douglas E. Brenneman, Ph.D.

The focus of this group is on the identification of substances that influence neurodevelopment in the mammalian central nervous system. Emphasis is on neuron-glia interactions that are mediated by peptides, and the isolation of novel neurotrophic agents. Current studies also include work on the role of excitatory amino acids in development, and an investigation of neuronal deficits associated with human retroviruses such as HIV.

- Unit on Neurophysiology and Biophysics—

Mark L. Mayer, Ph.D.

This group studies mechanisms controlling neuronal excitability, utilizing voltage-clamp and single channel recording from mammalian CNS neurons grown in cell culture. Both physiological and pharmacological approaches are used to characterize ion channel activity, with current emphasis on excitatory amino acid receptors. Experimental approaches range from fluctuation analysis and rapid perfusion techniques, to analysis of synaptic activity between pairs of neurons. Problems under analysis concern receptor classification, ion channel selectivity, and drug action at L-glutamate receptor subtypes.

- Section on Neuronal Secretory Systems—

James T. Russell, Ph.D.

This group studies the molecular and functional organization of the nerve terminal, using the hypothalamo-neurohypophyseal system as the model. The approaches employed include biochemical pharmacology, molecular biology, and high resolution image processing. The studies are aimed at the mech-

anisms of regulation of secretion by 1) modulation of ionic channels, and by 2) activation of receptors at the terminal. Studies are under way to characterize a transient K^+ channel involved in control of action potential kinetics. Studies are also carried out with respect to the organization of the peptidergic secretory vesicle core, which contains large concentrations of neuropeptides, and the vesicle membrane, which are essential in the cell biological processes of biosynthesis, storage, transport, and secretion of the neuropeptides.

- Section on Cellular Neurobiology—

Y. Peng Loh, Ph.D.

This section investigates the regulation and mechanism of biosynthesis of neuropeptides, at the transcriptional, translational and post-translational levels, in correlation with different physiological and developmental states in the animal model. The primary focus is on the ACTH/endorphin/ α -MSH family of peptides which are derived from a larger precursor form (pro-opiomelano-cortin), synthesized in the brain and pituitary gland. Studies concern the mechanism of neurotransmitter signal transduction from the cell surface receptor to the nucleus to modulate specific gene expression and subsequent message translation, as well as the enzymology of post-translational modification of the pro-neuropeptide, which ultimately defines the peptide product secreted by the cell. Techniques used include peptide chemistry, immunochemistry, light and electron microscopy, recombinant DNA technology, *in situ* hybridization, subcellular fractionation, and tissue culture.

Laboratory of Molecular Genetics—

Igor Dawid, Ph.D.

Investigators in this laboratory use the tools of molecular and cellular biology to answer questions about gene transmission and recombination, and the regulation of genetic functions during development. The range of model systems under investigation includes bacterial and animal viruses, transformed animal cells, yeasts, mouse and *Xenopus* embryos and the fruit fly *Drosophila melanogaster*. Recombinant DNA technology and gene transfer methods are emphasized.

- Section on Developmental Biology—
Igor Dawid, Ph.D.

Interest is focused on the molecular genetics of development. Gene expression during early embryonic stages of *Xenopus* is studied with the aid of cDNA libraries. Regulation of keratin gene expression provides an approach to the molecular analysis of ectoderm differentiation, and genes specific for early neural development are sought. Embryonic induction is studied at the molecular level. Genetic control of development is also studied in *Drosophila*. Two regulatory genes, *fs(1)h* and *trithorax*, have been cloned, and their products are studied with the aim of elucidating the regulatory interactions between such homeotic genes.

- Unit on Yeast Genetics—
Alan Hinnebusch, Ph.D.

The regulation of amino acid biosynthesis is studied in yeast, as a model of “global” genetic control pathways in eukaryotes. Regulatory genes and their products are isolated and their interactions studied. A novel translational control mechanism has been uncovered that governs the expression of a key positive regulator of transcription. *In vitro* mutagenesis and classical yeast genetics are applied to identify the messenger RNA sequences required for translational control and the regulatory proteins that interact with these sequences.

- Unit on Viral Gene Regulation—
Judith Levin, Ph.D.

Molecular mechanisms involved in the replication of a mammalian retrovirus, murine leukemia virus, are studied with the goal of understanding regulated expression of viral genetic information. Interest is focused on the process of reverse transcription and translational control mechanisms. Experimental approaches include isolation of viral genes and expression in bacteria, purification of the viral gene products, production of specific antisera, and mutational analysis to correlate gene structure with functional activity. Similar studies on the human retrovirus HIV have been initiated.

- Section on Molecular Regulation—
Michael Cashel, M.D., Ph.D.

Genes regulating the growth of *E. coli* respond to physiologic stress by coordinating transcription and translation of large sets

of genes in a way that insures cell survival. One such "global control" system is mediated by guanosine 3'5' bispyrophosphate (ppGpp). It is dissected by manipulating the expression of genes involved in synthesis, degradation, and sensitivity to ppGpp. This system affects amino acid biosynthesis, stable RNA synthesis, proteolysis, growth rate control, protein synthesis, and energy metabolism. Effects of ppGpp on gene expression and cell physiology are viewed as defining new roles of an intracellular hormone.

- Section of Microbial Genetics—

Robert Weisberg, Ph.D.

Mechanisms of genetic recombination are studied using bacteriophage lambda. Experiments proceed at the level of genetics, nucleic acid structure, and enzymatic reactions. Studies are conducted to isolate and analyze host factors and the genes that are required for site-specific recombination, and work is carried out to elucidate the molecular mechanisms of the reactions catalyzed by these host factors.

- Unit on Formation of RNA—

Robert J. Crouch, Ph.D.

Cell growth depends on highly specific interactions of proteins with nucleic acids. One such protein is the enzyme ribonuclease H (RNase H), which influences the ability of particular DNA-RNA hybrids to act as initiation sites for DNA replication. Interactions between RNase H and DNA-RNA hybrids are examined in human cells, in yeast and in bacteria using a wide range of molecular approaches. This group is currently studying the changes in cell growth which result from alterations in the intra-cellular concentration of RNase H (e.g., by using mutants which have low RNase H activity).

Laboratory of Mammalian Genes and Development—

Heiner Westphal, M.D.

Gene regulation in the living mammalian organism involves cell-cell interactions which become more and more complex as development proceeds. This laboratory studies gene regulation at specific stages of mouse development. The functions analyzed are encoded by normal or mutated chromosomal genes, or by transgenes that have been inserted in the mouse germ line.

- Section on Transgene Regulation—
Heiner Westphal, M.D.

Oncogenesis is the main topic of current research. Transgenic mice have been generated which synthesize oncogene products in the lens, a tissue with simple architecture and a well-studied developmental program. Events that follow the initial accumulation of oncogene products in specific cells of the embryonic lens vesicle are studied by *in situ* histology and biochemistry. Transgenic technology is also used to generate mouse models for human diseases, including AIDS and various genetic disorders.

- Unit on Molecular Embryology—
Kathleen A. Mahon, Ph.D.

The primary interest is in the elucidation, on the molecular level, of events which orchestrate the development of a multicellular mammalian organism from a one-cell embryo. The current focus is on the function of the murine homeobox genes, the most likely candidates for the genetic elements which regulate mammalian pattern formation. Strategies to isolate other developmentally important genes are also being pursued. Experimental approaches employ recombinant DNA technology, experimental embryology, gene transfer methodology, and genetic analysis.

Laboratory of Developmental Pharmacology—
Daniel W. Nebert, M.D.

Research in this laboratory has concentrated on attempts to understand drug-induced gene expression at the molecular level. This laboratory studies mechanisms of enzyme regulation, with particular reference to the induction of drug-metabolizing enzymes by environmental chemicals as well as drugs. There is particular interest in relationships between the genetic expression of these enzyme systems and fundamental biologic events such as teratogenesis, drug toxicity, carcinogenesis and mutagenesis. Other projects within this laboratory apply molecular biologic methods to problems in clinical pharmacology and pharmacogenetics. One long-range goal is to design molecular biology-based assays to predict the individual risk in humans of drug-induced birth defects and chemically-induced malignancies.

- Section of Pharmacogenetics—
Daniel W. Nebert, M.D.

Inbred strains of mice, transgenic mice and cells in culture are probed with recombinant DNA and ancillary techniques to study the regulation and gene expression of drug-metabolizing enzymes, with particular reference to the P-450 gene superfamily and [Ah] gene battery. Related research projects are in the areas of developmental biology, teratology, and the control on endogenous drug-metabolizing enzymes by hormones and other factors.

Laboratory of Developmental and Molecular Immunity—
John Robbins, M.D.

The laboratory conducts research into the developmental and molecular biology of “natural” and immunization-induced immunity to bacterial and other antigens. Emphasis has been placed on the study of pathogenic mechanisms, MHC and other antigenic molecules (including their purification and characterization), and on the immuno-regulatory mechanisms of the host. The hybridoma and recombinant DNA technologies, as well as the methods of macromolecular purification, have been applied to these problems.

- Section on Bacterial Disease Pathogenesis and Immunity—
John Robbins, M.D.

A primary objective of this group has been to develop a new generation of bacterial vaccines, and a specific goal to devise methods to increase the immunogenicity of the capsular polysaccharides of *H. influenzae* type b, pneumococci, and *E. coli* associated with invasive human diseases. Semisynthetic conjugates of these polysaccharides have been prepared which convert their immunogenic properties to those of T-cell independence. These conjugates are also used to characterize the ontogeny and genetic control of the serum antibody response in humans. The physical-chemical characteristics of the pertussis toxin, and their relation to this molecule's toxic and protective activities, are studied. Monoclonal antibodies to the subunits of the toxin are being used as probes for the cloning of the gene(s) involved in its synthesis.

- Section on Immunoregulation and Cellular Control—
Edgar Hanna, Ph.D.

This section studies the mechanisms by which microorganisms deregulate immune systems. Hybridomas and antigen-selected clones that express the various functions of the murine immune system *in vitro* have been established, including various subpopulations of regulatory T-cells. These models are used to define the cellular and molecular targets of microorganisms and their toxins. Investigations are also directed towards understanding the development, regulation, and efficacy of cytotoxic T-lymphocytes (CTL) in immunologically incompetent mice as secondary hosts.

- Section on Molecular Genetics of Immunity—
Keiko Ozato, Ph.D.

Studies on the mechanisms of expression of MHC class I genes are a major focus of this laboratory. These genes reflect developmental and tissue-specific control, and are regulated by cytokines, such as interferon and tumor necrosis factor. Trans-acting nuclear proteins that bind cis-acting regulatory DNA sequences are examined *in vivo* and *in vitro*, and their corresponding genes are characterized. Mutations are introduced into the cis-acting sequences to identify the requirements for protein binding and functional activity. A variety of molecular and immunologic methods are used to analyze the structure and function of the trans-acting proteins and the genes. Synthetic peptides that correspond to certain domains of MHC class I antigens are studied to elucidate the basis of allo-responses and interaction with T cells. Studies are under way on several proto-oncogenes that are known to regulate MHC and other immunologically important genes.

Laboratory of Theoretical and Physical Biology— David Rodbard, M.D.

⁴¹ This laboratory conducts a wide range of multidisciplinary and theoretical studies, applying mathematical, statistical, and computer-based techniques to the analysis of complex clinical, biological, biochemical and pharmacological problems. Experimental work in the laboratory involves the study of receptors for drugs, hormones and neurotransmitters; the pharmacokinetics of calcium, cortisol, glucose, vitamin D, and testosterone in man; and the physical-chemical characterization of

proteins, nucleic acids, and viruses using polyacrylamide gel electrophoresis and related approaches.

- Section on Theoretical Biology—

David Rodbard, M.D.

This section has been concerned with the development of methods for characterization of complex receptor systems for drugs, hormones and neurotransmitters. Mathematical and biological approaches have been used to characterize multiple types and subtypes of receptors for opioids, and the “sigma” and phencyclidine (PCP) receptors in the brain. Refined computer analysis is used for mathematical modeling (simulation and curve fitting) to optimize experimental design and provide objective, quantitative interpretation of results. The section also develops new biostatistical methods to facilitate clinical research (e.g., generalized dose-response curve analysis and detection of pulses of hormone secretion).

- Section on Macromolecular Analysis—

Andreas Chrambach, Ph.D.

This section is concerned with the physical characterization (size, shape, conformation, malleability, and surface net charge) of biological particles such as nucleic acids, proteins, charged polysaccharides, cellular vesicles, viruses and crosslinked immunogens, and the isolation of post-translational forms of proteins. For that purpose, optimized gel electrophoretic methods are being developed, with optimization based on physical measurement and separation theory, made practical through incorporation into user-friendly computer programs. Recent applications include: 1) separation of DNA-protein complexes differing only in the location of the protein binding site on the DNA fragments, 2) the detection of “abnormal DNA” deviating from the common proportionality between electrophoretic mobility and size, and 3) the characterization of semi-synthetic immunogen preparation by their size and net charge.

- Section on Metabolic Analysis and Mass Spectroscopy—

Alfred L. Yergey, Ph.D.

This section develops novel techniques in mass spectrometry to permit high sensitivity studies of neurotransmitters, steroids, amino acids, and metals such as calcium. Stable (non-radioactive) isotope tracers are employed to investigate the

kinetics of metabolism of these species in man, and the time course of serum concentrations of these isotopes is measured by mass spectrometry and analyzed using computer models of compartmental distribution.

Endocrinology and Reproduction Research Branch—

Kevin J. Catt, M.D., Ph.D.

Current research is focused on the mechanisms controlling hormone secretion and action, with particular reference to hypothalamic-pituitary hormones and their receptor-mediated responses in endocrine target cells. This work includes the analysis of structure-function relationships displayed by peptide and glycoprotein hormones, and studies on the receptors and actions of hypothalamic peptides (GnRH, somatostatin, CRF, GRF), angiotensin II, ACTH, prolactin, and gonadotropins. The characterization and isolation of peptide hormone receptors, clarification of plasma-membrane related second messenger systems, and further elucidation of the control of steroidogenesis and glycogen synthesis, and major goals of the branch research program.

- **Section on Hormonal Regulation—**

Kevin J. Catt, M.D., Ph.D.

Receptor-mediated aspects of peptide hormone action are analyzed in target tissues regulated by hypothalamic peptides, angiotensin II, and gonadotropins. The receptors and mechanisms of peptide hormone action are investigated in isolated pituitary cells (GnRH, CRF, GRF, angiotensin II), adrenal cells (ACTH, angiotensin II), and steroidogenic cells of the ovary (LH, FSH, prolactin, GnRH). In these target cells, the roles of cyclic nucleotides, calcium-dependent pathways, and phosphoinositide metabolites, are studies in relation to the control of cellular activity and secretory processes by the regulatory hormones.

- **Section on Endocrine Physiology—**

Greti Aguilera, M.D.

This section investigates the mechanisms of regulation of mineralocorticoid secretion and circulatory homeostasis, as well as neuroendocrine mechanisms of adaptation to stress. Research includes *in vivo* and *in vitro* studies on the activation mechanisms and interactions of hormonal regulators in the control of adrenal and vascular sensitivity to angiotensin II.

The receptor-mediated actions of angiotensin II, corticotropin releasing factor, and other stress-related hormones in the central nervous system and pituitary gland are also investigated during normal hormone regulation and stress.

- Section on Molecular Endocrinology—

Maria Dufau, M.D., Ph.D.

This section investigates the molecular basis of peptide hormone action, with emphasis on the control of gonadal function. The laboratory analyzes the structure and function of gonadotropin receptors, and the hormone-regulated membrane coupling and intracellular events involved in the modulation of steroid biosynthesis. Current studies also include cell-to-cell communication in the testis, developmental aspects of Leydig cell maturation, and induction of regulatory mechanisms in the Leydig cell and their influence on other testicular compartments. This group also investigates the biological properties of stored and circulating gonadotropins in physiologic regulation and in clinical disorders of pituitary and gonadal function.

- Section on Molecular Structure and Protein Chemistry—

Hao-Chia Chen, Ph.D.

Research is conducted in the area of structural analysis, chemical synthesis, and modification of molecules important to reproductive and developmental biology. Major emphasis is placed upon the elucidation of structural requirements for biological activities, e.g., agonism or antagonism of hypothalamic, pituitary and placental hormones. The effect of divalency of polypeptide hormones on their biological activities, as well as the design of synthetic antigens for the development of immunological assays and detection of gene products, are also under investigation.

- Section on Adrenal Cell Biology—

Charles A. Strott, M.D.

Research is performed on the hormonal and molecular events responsible for adrenal steroid biosynthesis and secretion in mammals, using the comparative approach. Current studies include the identification and purification of specific steroid-binding proteins in the adrenal cortex, the role of the cytoskeleton in steroidogenesis, protein phosphorylation-dephosphorylation reactions, lipoprotein receptor activity,

cholesterol metabolism, and the differential structure and function of the zones within the adrenal cortex.

- **Section on Metabolic Regulation—**

Kuo-Ping Huang, Ph.D.

This section investigates the role of protein phosphorylation in the regulation of cellular differentiation, metabolism, receptor function, and gene expression. Several protein kinases involved in various signaling pathways are characterized to determine their mechanism of activation, cellular and subcellular distribution, and developmental expression. Current emphasis is devoted to protein kinase C, a key enzyme in the phosphoinositide signaling pathway. Activation of this enzyme in response to hormones, growth factors, neurotransmitters, phorbol esters, and antigens is characterized in neurons and other secretory cells. The role of protein kinase C in stimulus-response coupling is monitored by the phosphorylation of cellular proteins and the accompanying physiological changes. Mutant cell lines deficient in various protein kinases are used to determine the physiological function of these enzymes. Biochemical, immunological, and recombinant DNA techniques are employed in all of these studies.

- **Cell Biology and Metabolism Branch—**

Richard D. Klausner, M.D.

Research is directed toward an understanding of the structure, function, cell biology and genetic regulation of receptors; and to clarify developmental aspects of intracellular structure and function. Various methods are utilized to study receptor biosynthesis, dynamics, regulation, and degradation, using three different models: the transferrin receptor, the T-cell antigen receptor, and the interleukin-2 receptor. The branch also conducts clinical research on the fundamental mechanisms and treatment of patients with genetic disorders of iron metabolism (hemochromatosis) to learn how the intracellular traffic of iron is normally controlled, and at what level iron metabolism is abnormally regulated in such patients.

- **Section on Organelle and Receptor Structure and Function—**

Richard D. Klausner, M.D.

The T-cell antigen receptor serves as a model of a complex receptor signalling system. Four aspects of this receptor are studied: 1) The structure of the multisubunit structure is

defined by biochemical and molecular genetic techniques. Cloning of the genes encoding the receptor subunits allows a detailed analysis of receptor structure and the regulated expression of these genes; 2) Receptor mediated signal transduction is explored. In particular, the mechanisms and consequences of the activation of tyrosine-specific kinases and phosphatases are studied using biochemical, enzymatic and recombinant DNA approaches; 3) This receptor is critical to the immune response. Thus, its role in thymic development, T-cell responsiveness and T-cell unresponsiveness is studied in terms of both the structure and signalling properties of the receptor. 4) The seven chains of the T-cell receptor complex provide an unique opportunity to understand the cell biologic processes that govern how multichain complexes are assembled and correctly transported through the cell. A complex picture of the relationship between intracellular targeting, assembly and different pathways of degradation is emerging. A wide array of biochemical, immunological and cell biologic approaches are focused on this problem, and stable transfectants of isolated receptor component genes are also utilized.

- Unit on Molecular Immunology—

Warren J. Leonard, M.D.

Research is focused principally on the human interleukin-2 receptor, which plays a key regulatory role in the T-cell immune response. The high affinity receptor consists of at least two proteins (p55 and p70). p55 has been cloned, and currently this group is analyzing the regulation of expression of the gene. Deletion mutants in the promoter region are analyzed, and DNA binding proteins have been detected. There is a particular interest in characterizing the regions responsible for responsiveness to phorbol myristate acetate and the transactivator (p40x) protein product of HTLV-1. Work on p70, which is critical in IL-2 mediated signal transduction, is focused on protein purification and characterization. Efforts to prepare antibodies and clone cDNAs are in progress. The group also is studying two activation cDNAs whose corresponding mRNAs is expressed rapidly following T-cell activation. (One may be a newly identified cytokine.) A wide range of methods of molecular biology, biochemistry, and cellular immunology are employed.

- Unit on Receptor Regulation—

Joe B. Harford, Ph.D.

This group studies the mechanisms by which eukaryotic cells modulate the expression and/or function of receptors. The regulation of the human transferrin receptor is the major focus; this receptor serves as the principle means by which cells acquire iron, and it is regulated by iron availability. The transferrin receptor is also modulated by changes in the state of growth and differentiation. The techniques of cell and molecular biology address the mechanisms by which receptors are regulated. The human transferrin receptor is regulated at both the transcriptional and post-transcriptional levels. Detailed structural and mechanistic studies of genomic elements that regulate transcription, and of sequences within the mRNA that regulate message levels, make this highly regulated and critical cellular receptor an excellent model of genetic regulation of receptor expression.

- Unit on Translational Control—

Richard D. Klausner, M.D.

Research in this group focuses on a poorly understood but widely used and critical locus of eukaryotic gene expression—translation. Studies have been centered around a genetic approach, using recombinant DNA techniques to determine how the translation of specific mRNA species can be regulated. The message for human ferritin, which is highly translationally regulated, is used as a model. The genetic element responsible for the reversible regulation of the translation of this mRNA has been identified and termed IRE (iron responsive element). Current research is concentrating on detailed structure of this RNA element and the identification and isolation of proteins that recognize this specific genetic structure. The roles of IRE's and IRE-like elements in the regulation of other gene products and in the regulation of general translation are studied.

Harald Löe, D.D.S., Dr. Odont.

Director

Abner L. Notkins, M.D.

Director, Intramural Research

Bruce J. Baum, D.M.D., Ph.D.

Clinical Director

The National Institute of Dental Research recruits about one or two dental and one or two medical staff fellows each year. Initial assignments are for 2 years and may be extended for a third year. Appointments for medical staff fellows usually begin on July 1 and for dental staff fellows on August 1. Selection of candidates is based on program needs and qualifications of candidates. The branch and section chiefs screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research positions will be made following personal interviews by laboratory and branch chiefs who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chief are listed below. A brief sketch of each research area is provided.

Dental Staff Fellows

Dental staff fellows spend much of their first year (about two-thirds) providing a wide range of care for patients at the Clinical Center. The remaining time is spent in clinical or laboratory research. The second (and third) year will be spent primarily (about 80 percent) engaged in supervised research with some clinical care responsibilities. Dental staff fellows must have a dental licensure in the United States, a minimum of 1 year hospital dental experience, and a desire for a career in academic dentistry. Prospective applicants desiring more information should write to Bruce J. Baum, D.M.D., Ph.D., Clinical Director, NIDR, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows

The medical staff fellow program focuses on inflammatory and infectious disorders with an emphasis on auto-immune diseases, antiviral chemotherapy and viral diseases. The medical staff fellow will receive training in the design, execution and

analysis of clinical trials and will receive laboratory training utilizing the latest techniques in immunology, molecular biology and/or cell physiology. Applicants must be board eligible in internal medicine, infectious disease, rheumatology or allergy and clinical immunology, and have a license to practice medicine in the United States. Prospective applicants desiring more information should write to Bruce J. Baum, D.M.D., Ph.D., Clinical Director, NIDR, National Institutes of Health, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of NIDR programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Clinical Research Branches

Diagnostic Systems Branch—

Urs E. Ruttiman, Ph.D., Acting

Investigations are directed toward research and development of diagnostic techniques. Specific emphasis is placed on radiologic and other noninvasive analysis techniques. The main focus is on interdisciplinary investigations linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement, and new geometric bases for quantitative analysis of tissue morphology.

Neurobiology and Anesthesiology Branch—

- Clinical Pain Section—

Ronald Dubner, D.D.S., Ph.D., Chief

Mitchell Max, M.D., Clinical Coordinator

This section is the core group in the multi-institute NIH pain research program. The medical staff fellow will conduct research on the neural mechanisms and neuropharmacology of pain and analgesia in patients with nerve injury, cancer, arthritis, low back pain, or post-operative pain. Recent areas of study have included the analgesic effects of serotonin agonists, kappa and delta-receptor opiates, bradykinin inhibitors,

adrenergic agonists, and tricyclic antidepressants; the mechanisms of analgesia produced by periventricular gray stimulation in patients with chronic pain; the characterization of the disturbances in nerve function responsible for neuropathic pain; and the neural and psychological mechanisms of placebo and hypnotic analgesia. Fellows will receive intensive training in statistics, study design, and the use of experimental pain techniques in human subjects. The fellowship includes the pain management consultation service for the NIH Clinical Center, and close interaction with a large basic science group.

Epidemiology and Oral Disease Prevention Program—

- Office of the Director—
Harald Löe, D.D.S., Acting Director
Thomas F. Drury, Ph.D., Deputy Director
- Office of Program Support—
Thomas F. Drury, Ph.D., Acting Chief
- Microbial Systematics Section—
Micah I. Krichevsky, Ph.D., Chief
- Epidemiology Branch—
James P. Carlos, D.D.S., M.P.H., Chief
- Caries Section—
James P. Carlos, D.D.S., M.P.H., Acting Chief
- Periodontal Diseases Section—
Harald Löe, D.D.S., Acting Chief
- Soft Tissue, Craniofacial Defects, and Pain Section—
Dushanka V. Kleinman, D.D.S., M.P.H., Chief
- Analytical Studies Branch—
L. Jackson Brown, D.D.S., Ph.D., Chief
- Disease Prevention and Health Promotion Branch—
William S. Driscoll, D.D.S., M.P.H., Acting Chief
- Health Promotion Section—
Helen C. Gift, Ph.D., Chief
- Disease Prevention Section—
William S. Driscoll, D.D.S., M.P.H., Chief

This program plans, develops and directs the application of epidemiologic methodologies to investigate oral diseases and disorders, including dental caries, periodontal diseases, soft

tissue diseases, craniofacial defects and a broad spectrum of pain syndromes. Research is conducted on the effects of temporal variations in oral disease patterns on dental education, dental research and dental care delivery systems. Clinical, field, demonstration and other studies related to the prevention of oral diseases and disorders are carried out. The program also develops health education on oral disease prevention. Programs also implement the scientific transfer of research findings.

Clinical Investigations and Patient Care Branch—

Bruce J. Baum, D.M.D., Ph.D.

- Patient Care Section—
Michael W. Roberts, D.D.S., M.S.D.
- Clinical Studies Unit—
Philip C. Fox, D.D.S.

This branch conducts clinical studies which emphasize exocrine, sensory, and motor performance in several patient groups. Primary interest focuses on the evaluation and management of sicca syndrome, an autoimmune exocrinopathy. Studies directed at treating both the salivary and immune components of this disease are ongoing. Considerable effort is also directed at a common complication of salivary dysfunction, oropharyngeal dysphagia, using ultrasonography as a primary diagnostic tool. Study of oral sensory performance (including, gustatory, olfactory, thermal, tactile, and textural discrimination) is directed at function across the lifespan (aging) and at persons with salivary hypofunction. Severely compromised patients (irradiated, chemotherapy, AIDS) are studied with respect to their exocrine protective mechanisms, mucosal barrier function, and susceptibility to oral opportunistic infections.

Basic Research Laboratories

Laboratory of Cellular Development and Oncology—

John E. Folk, Ph.D.

- Bone Cell Biology Section—
A. Haridara Reddi, Ph.D.
- Enzyme Chemistry Section—
John E. Folk, Ph.D.
- Molecular and Cellular Biology Section—
Keith Robbins, Ph.D.

Research is directed toward an understanding of normal and aberrant cell growth. Emphasis is placed upon hard tissue development, general protein biosynthesis, and oncogenesis. Topics of current study include: mechanisms of bone formation in physiological models of fracture healing and new bone formation; the role of osteogenin, a protein factor that initiates bone differentiation; structure and function of the transglutaminases, enzymes that catalyze posttranslational crosslinking of protein molecules; the biosynthesis, regulation and mechanism of action of eukaryotic protein initiation factor 4D; identification of oncogenes and elucidation of their roles in normal cell development and carcinogenesis; and the mechanisms by which polypeptide growth factors control cell growth. Our advances and understanding arise from the laboratory's expertise in the disciplines of cell biology, molecular biology, molecular genetics, developmental biology, enzymology, immunochemistry, and protein chemistry.

Clinical Investigations and Patient Care Branch—

Bruce J. Baum, D.M.D., Ph.D.

- Clinical Investigations Section—
Bruce J. Baum, D.M.D., Ph.D.
- Membrane Transport Unit—
R. James Turner, Ph.D.

Laboratory investigations by this branch focus on neurotransmitter regulation of secretory events in water transporting exocrine epithelial cells and their perturbation by pharmacologic agents or pathologic conditions. Studies directed at fluid secretion focus on the mechanism and control of Cl^- and Ca^{2+} movements across plasma membranes. Additionally Ca^{2+} fluxes across intracellular membranes are studied. Investigations directed at protein secretion focus on neuroreceptor regulation

of transcriptional, post-translational and exocytotic events. Model preparations employed include cultured epithelial cells, dispersed acini and specific surface membrane vesicles, while the investigative approach is biochemical, molecular and cell biological.

Bone Research Branch—

John D. Termine, Ph.D.

- Proteoglycan Chemistry Section—
Vincent C. Hascall, Ph.D.
- Mineralized Chemistry and Structure Section—
Edward D. Eanes, Ph.D.
- Skeletal Biology Section—
John D. Termine, Ph.D.
- Protein Biophysics Unit—
Dennis A. Torchia, Ph.D.

The Bone Research Branch studies the structure, development, biosynthesis and regulation of bones, teeth and cartilaginous tissues. Emphasis is given to studies of acquired and heritable disorders of the skeleton. Branch scientific disciplines encompass cell biology, molecular biology, protein and carbohydrate biochemistry, immunochemistry and molecular biophysics. Areas of study include: bone and cartilage cell biology; skeletal stem cell differentiation; regulation of skeletal tissue metabolism; structure and function of matrix macromolecules such as collagen, the proteoglycans and osteonectin; organization and structure of connective tissue using nuclear magnetic resonance spectroscopy; physical chemical characterization of hard tissue minerals and synthetic mineral formation systems; and mechanisms of bone formation in physiological models of fracture healing.

Laboratory of Developmental Biology and Anomalies—

Yoshihiko Yamada, Ph.D., Acting

- Cell Biology Section—
Hynda Kleinman, Ph.D.
- Molecular Biology Unit—
Yoshihiko Yamada, Ph.D.

The laboratory emphasizes cellular and molecular approaches to study the role of the extracellular matrix in

development, disease, and wound healing. Research projects focus on cartilage, basement membranes, extracellular matrix receptors, tumor metastasis and impaired wound healing. Recombinant DNA technology is used to study gene regulation and protein structure and function. Transgenic mice are used to study both gene expression and protein function and to generate animal models for disease. Medical staff fellows in this laboratory are encouraged to pioneer new research areas.

Laboratory of Immunology—

Stephan E. Mergenhagen, Ph.D.

- Cellular Immunology Section—
Sharon M. Wahl, Ph.D.
- Clinical Immunology Section—
Reuben P. Siraganian, M.D., Ph.D.

The laboratory conducts research on the molecular basis of immunologically-mediated acute and chronic inflammatory diseases. More specifically, research is focused on the contributions of mononuclear leukocytes and cytokines to the regulation of connective tissue catabolism, tissue repair and inflammation and to the development of chronic inflammatory diseases which include the Acquired Immune Deficiency Syndrome, Rheumatoid Arthritis and Chronic Periodontitis. Research on the immediate hypersensitivity reaction utilizes molecular biological technologies to define receptors on basophils and mast cells for Immunoglobulin E and explores the biochemical pathways that are involved in cell secretion. While a dental or medical staff fellow is assigned to work under a senior investigator, considerable opportunity exists for collaboration with scientists in other components of the Laboratory of Immunology.

Laboratory of Microbial Ecology—

Bruce M. Chassy, Ph.D., Acting

- Microbiology Section—
Jack London, Ph.D., Acting
- Pathogenic Mechanisms Section—
Ann Sandberg, Ph.D.

Research in microbial ecology is focused on understanding mechanisms of bacterial pathogenesis. The laboratory uses a

broad inter-disciplinary approach in studies on: the colonization of the oral cavity, in particular the periodontium, by bacteria; the molecular basis of bacterial adhesion to other bacteria, as well as to hard and soft tissues; the biochemistry, physiology and genetics of oral bacteria; the nature of the inflammatory processes provoked by bacteria; and the mechanisms of host response to acute and chronic bacterial challenges. Specific research programs include: application of recombinant DNA techniques to understanding microbial metabolic traits, adhesins, and surface receptors; biochemical characterization of key enzymes and transport systems, adhesins and receptors; the immunology and immunochemistry of cell-cell and cell-tissue interactions; and the mechanism of polymorphonuclear leucocyte-mediated recognition and killing of bacteria.

Laboratory of Oral Medicine—

Abner Louis Notkins, M.D.

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (herpes simplex), with emphasis on recombinant DNA technology; virus-induced immunopathology; the role of certain B-lymphocyte subsets in the pathogenesis of autoimmune disorders; the etiology of various dermatologic disorders, including aphthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (Sjogren's syndrome and salivary gland tumors) and endocrine glands (diabetes mellitus); the use of the transgenic mouse model to study the pathogenesis of viral and autoimmune disorders; and double-blind clinical trials to evaluate the effectiveness of various antiviral and anti-inflammatory agents in the treatment of oral lesions.

Neurobiology and Anesthesiology Branch—

Ronald Dubner, D.D.S., Ph.D.

- **Neural Mechanisms Section—**

Ronald Dubner, D.D.S., Ph.D.

Research on peripheral and central nervous system mechanisms of oral-facial sensation is performed by this laboratory.

In one major series of studies, behavioral responses in monkeys trained in pain and temperature discrimination tasks are correlated with single-cell neuronal activity recorded in the medullary dorsal horn, thalamus and cerebral cortex. Correlative electrophysiological and morphological studies examine the characteristics of single cells in the dorsal horn and relate their function to morphology and neuronal circuitry. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions.

Other studies are examining the effects of nerve damage on neuro-chemical mediators in the dorsal horn utilizing radioimmunoassay, immunocytochemistry and molecular biology approaches. In addition, electro-physiological methods are used to examine changes in dorsal horn neuronal activity following such nerve lesions.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Lawrence E. Shulman, M.D., Ph.D.

Director

Henry Metzger, M.D.

Director of Intramural Research

John H. Klippel, M.D.

Clinical Director

Appointments in Clinical Research

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) offers a variety of training programs principally at the post-doctoral level. Medical Staff Fellowships are awarded primarily to those physicians wishing to pursue combined clinical and laboratory training. The fellow works under the guidance of one of the senior investigators in the Arthritis and Rheumatism Branch. With rare exception only those having completed at least 2 years of residency are appointed. The appointment is for 2-3 years and the training fulfills the requirements for the Rheumatology Subspecialty Board Examination. The Institute offers other training opportunities for those with MD or other doctorate degrees in the Arthritis and Rheumatism Branch as well as in the Laboratory of Physical Biology. For further information write Director, Intramural Research, Building 10, Room 9N240, NIAMS, NIH, Bethesda, MD 20892.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIAMS programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Clinical Research Branches

Arthritis and Rheumatism Branch—

• Clinical Investigations—

John H. Klippel, M.D.

Paul H. Plotz, M.D.

Alfred D. Steinberg, M.D.

Ronald L. Wilder, M.D., Ph.D.

James E. Balow, M.D. (NIDDK)

Howard A. Austin, M.D. (NIDDK)

Branch-wide clinical studies involve patients with systemic lupus erythematosus, polymyositis or rheumatoid arthritis. Patients participate in protocols evaluating new pharmacologic

agents or apheresis. In addition, patient blood and tissue specimens are analyzed to reveal pathogenetic mechanisms.

- **Laboratory Investigations**

- Section on Cellular Immunology—

Alfred D. Steinberg, M.D.

The section conducts studies on the bases for autoimmune diseases in mice and humans with emphasis on systemic lupus erythematosus using classical genetics, molecular biological and cellular immunological techniques.

- Section on Chemical Immunology—

Henry Metzger, M.D.

This section is studying mast cell secretion mediated by the high-affinity receptor immunoglobulin E. The studies involve isolation, characterization, and reconstitution (into liposomes) of the receptor and exploration of biochemical perturbations during triggering. This system serves as a powerful model for examining at a molecular level the proximal events in cellular secretion mediated by a cell-surface receptor.

- Section on Chemical Immunology—

Henry Metzger, M.D.

Jean-Pierre Kinet, M.D.

This section is studying the receptor for IgE as a model for examining, at the molecular level, the proximal events in cellular secretion mediated by a cell-surface receptor. Molecular-genetic and protein chemical techniques in particular are used to probe the relationship of structure to function.

- Section on Connective Tissue Disease—

Paul H. Plotz, M.D.

Ronald L. Wilder, M.D., Ph.D.

This section studies the etiologic and pathogenetic basis of autoimmunity (lupus, psoriatic arthritis, rheumatoid arthritis, polymyositis) by investigations of patients and animals. The role of viruses and bacteria in these illnesses is studied, using cellular, molecular, biological, immunological and pharmacological techniques.

Laboratory of Physical Biology—

- **Muscle Biophysics Section—**

R.J. Podolsky, Ph.D.

M. Schoenberg, M.D.

L.C. Yu, Ph.D.

This section studies the mechanism of muscle contraction in intact cells and in simplified preparations using X-ray diffraction, high time resolution mechanochemical techniques, and radiation inactivation analysis of physiologic function.

- **Macromolecular Biophysics Section—**

E. Kempner, Ph.D.

N. Gershfeld, Ph.D.

M. Murayama, Ph.D.

This section investigates lipid dispersions in water as models of the structure and physical states of lipids in cell membranes. The actions of ionizing radiation on macromolecules are used to determine the *in vivo* size of the functional units for different biological activities (hormone receptors, enzyme complexes, and regulatory units). Aggregation of blood platelets is studied under various conditions.

- **Structural Biology Section—**

A.C. Steven, Ph.D.

This section studies mechanisms of macromolecular assembly and structure-function relationships at the supramolecular level by means of high resolution microscopy in conjunction with digital image processing. Computer modeling is also used to integrate data from other biochemical and biophysical sources. Systems of interest include animal and bacterial viruses, keratin filaments, and other fibrous polymers and oligomeric protein complexes.

- **Orthopedic Research Unit—**

Mark Bolander, M.D.

Work in the Orthopedic Research Unit includes studies on regulation of gene expression in fracture healing and on the structure of osteonectin.

David P. Rall, M.D., Ph.D.
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biologic factors in the environment that can adversely affect people, to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents, and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within people on the susceptibility to and course of disease induced by these agents. In addition, the Institute maintains an active research program in basic biomedical sciences.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 13 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. The relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Medical Staff Fellows

Medical staff fellows work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each fellow will work directly under a senior scientist in an area of research chosen by the fellow and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, medical staff fellows may work out informal arrangements with

the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIEHS Divisions participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Division of Intramural Research

—John A. McLachlan, Ph.D.

The Division of Intramural Research conducts fundamental studies in diverse areas of biomedical research. Possibilities for collaboration abound between Institute laboratories and divisions as well as with nearby medical institutions. Brief descriptions of the laboratories and their research programs are given below.

Laboratory of Cellular and Molecular Pharmacology—James W. Putney, Jr., Ph.D.

Research is aimed at understanding the mechanisms that govern toxic reactions to exposure by harmful chemicals present in the environment. Many biological systems are not sufficiently understood to allow for mechanistic conclusions to be drawn from results of experiments involving the direct use of toxic agents. Emphasis is placed upon basic research aimed at defining certain biological systems at the molecular level, with particular attention on regulatory mechanisms. Research programs study membrane function. Studies on the metabolism of environmental chemicals by membrane-bound enzymes, the transport of solutes across epithelial membranes and the modification of cellular responses by surface membrane receptors are under way. Research includes investigation to understand the operation of the systems at the molecular level; to determine the mechanisms by which various toxicants perturb these systems; and to enumerate the implications of such interactions on human health. Specific areas of research include: studies on cellular signal transduction mechanisms with emphasis on the functions of

guanine nucleotide-dependent regulatory proteins in receptor mechanisms, and on the regulation of cellular Ca^{2+} metabolism through inositol phosphate metabolism and phosphorylation of specific membrane channels for Ca^{2+} ; investigations into the molecular species of membrane-bound drug metabolizing P-450 enzymes, with emphasis on the role of molecular microheterogeneity in determining species and tissue specific toxicity; studies on the transport functions of membranes, emphasizing the mechanisms by which drugs and other xenobiotics are conveyed across various biological barriers.

Laboratory of Reproductive and Developmental Toxicology—

John A. McLachlan, Ph.D.

This laboratory works at the interface of reproductive sciences and environmental biology and medicine. Research includes studies on: the molecular and cellular biology of steroid hormone receptors including their ontogeny; the pharmacology of synthetic and natural hormones; the regulation and structure of genes encoding steroid metabolizing enzymes; estrogen actions at the molecular and cellular levels; differentiation of the mammalian reproductive system; male germ cell differentiation; peptide growth factor biology; uterine biology; hormonal carcinogenesis; and genital tract biology and pathology. Opportunities exist for collaboration. Collaborative projects in clinically-related disciplines may be available with local medical schools.

Laboratory of Molecular and Integrative Neuroscience—

Andres Negro-Vilar, M.D., Ph.D.

The laboratory studies the basic mechanisms mediating brain regulation of neuroendocrine, cognitive and behavioral functions, to elucidate the complex interactions between the brain and the environment that result in normal or abnormal neural activity. Neuroendocrine regulation and signal transduction are explored using modern molecular and cell biology techniques. The integrative role of neuropeptides in regulating central and peripheral events is studied, offering opportunities for an interdisciplinary, multifaceted approach. The encoding of messages in pulsatile peptide secretion and the role of pulsatility in modulating neural, endocrine and reproductive

functions is studied using *in vivo* and *in vitro* models. Regulation and interactions between neuropeptides and neurotransmitters are analyzed at the cellular and molecular level, to evaluate the functional role of peptides in extra-pyramidal disorders, epilepsy or stress responses. Novel peptides isolated from tissues and biological fluids are studied, to uncover their biological activities in central and peripheral organs. Specific neurotoxins are employed to develop animal models for neurodegenerative processes, including alterations in cognitive and motor function. Collaborative clinical studies are conducted in reproductive neuroendocrinology and in other areas.

Laboratory of Pulmonary Pathobiology—

Paul Nettesheim, M.D.

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Laboratory of Molecular Biophysics—

Colin F. Chignell, Ph.D.

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high-pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials, and their metabolites emphasize biomechanism elucidation.

Laboratory of Genetics—

Burke H. Judd, Ph.D.

The laboratory investigates the molecular structure and the expression and regulation of eukaryotic genes. It also develops systems for detection of spontaneous and induced mutations in mammalian systems.

Laboratory of Molecular Genetics—

Charles H. Langley, Ph.D.

The laboratory utilizes molecular biological techniques to study three areas of genetics. The molecular basis of replication, recombination and repairs of the genome is investigated in diverse *in vivo* and *in vitro* model systems from prokaryotes and eukaryotes. Research is directed toward understanding the relationship of gene structure and function in development. *Drosophila* is the model system in these endeavors. The relative roles of mutation, recombination and selection in shaping molecular genetic variation found within populations and during evolution is studied. Their research involves both theoretical and experimental projects.

Laboratory of Molecular Carcinogenesis—

J. Carl Barrett, Ph.D.

The overall goal of this laboratory is to understand the genes involved in carcinogenesis, including proto-oncogenes and tumor suppressor genes, and to elucidate the mechanisms by which environmental substances affect these genes. The research includes: 1) cloning and characterizing tumor suppressor genes; 2) understanding the interactions between oncogenes and tumor suppressor genes; 3) defining the normal function of tumor suppressor genes in growth and differentiation; 4) cloning transforming genes from human and rodent mesotheliomas; and 5) understanding the factors involved in the susceptibility of different individuals to carcinogenesis.

Division of Biometry and Risk Assessment—

—David G. Hoel, Ph.D.

The Division of Biometry and Risk Assessment plans and conducts basic and applied research in the areas of quantitative and biochemical risk assessment, statistics, biomathematics, epidemiology, and molecular modeling. The qualitative

and quantitative estimation of adverse health effects resulting from exposure to hazardous environmental agents, with particular emphasis on the development of methodology useful in this estimation process, is studied. The identification of environmental risk factors and the elucidation of the biological mechanisms that underlie their action also is studied. The Division also provides statistical, mathematical, data processing, and computer engineering and use support to other programs of the Institute, and assists the Office of the Director in addressing specific health issues that bear on the welfare of the general public. The unique combination of biomathematicians, statisticians, epidemiologists, biochemists, and molecular toxicologists in a single, unified research program permits the multidisciplinary approach that is required to resolve the many complex issues involved in the identification, evaluation, and characterization of environmentally related human health risks.

Molecular Modeling Section—

The Molecular Modeling Section is concerned with determining theoretical factors involved in mutagenesis and the initial steps of carcinogenesis. Quantum chemistry to examine the physical chemical factors (charge distributions, binding energies, stereochemistry, activation energies, solvation, counterions) contributing to site specificity of DNA damage by chemical agents is under way. The techniques are employed to determine changes in molecular properties of oncogene proteins as a consequence of specific mutations.

Statistics and Biomathematics Branch—

David G. Hoel, Ph.D.

The Statistics and Biomathematics Branch conducts a broad research effort focused on statistical and mathematical aspects of environmental health issues, and provides statistical and computational support for various research projects within other Divisions of the Institute. Major areas of research interest include the adaptation and development of statistical methodology applicable to experimental design and analysis problems in toxicology and epidemiology, and the utilization of mathematical theory in addressing quantitative issues associated with the modeling of biological processes. Much of the current

research effort has been motivated by problems in theoretical population genetics, genetic toxicology, and risk assessment.

Epidemiology Branch—

Walter J. Rogan, M.D.

The Epidemiology Branch carries out field studies of chronic diseases and environmental risk factors in order to determine the degree to which some of the major causes of mortality and morbidity in this country are related to or aggravated by potentially hazardous environmental exposures. Branch researchers are also concerned with the effects of environmental toxins on reproduction and development, with development of sensitive analytical methods for assessing these effects, and with general adaptation and application of laboratory screening procedures to the monitoring of human populations.

Laboratory of Biochemical Risk Analysis—

George W. Lucier, Ph.D.

The Laboratory of Biochemical Risk Analysis conducts a broadly based, experimental research program concerned with improving the biological basis for and reducing the uncertainties involved in the qualitative and quantitative estimation of human health risks. Research includes the role of chemical-induced DNA damage and cell replication in carcinogenesis; the activation of cancer-causing genes (oncogenes) in both human and animal model systems and its implications for risk assessment; the validation of biomarkers of exposure and effect; and the evaluation and comparison of metabolic activation/deactivation pathways for chemicals in human samples and animal model systems.

Computer Technology Branch—

Arthur G. Cullati

The Computer Technology Branch, which is responsible for developing overall strategies for computing at the Institute, manages and operates the Institute's central computer system; coordinates all data communications and networking activities; develops laboratory computer, scientific and administrative information systems; manages the Institute's word processing, office automation, and workstation activities; and provides a full range of user services to Institute personnel.

Division of Toxicology Research and Testing

—Richard A. Griesemer, D.V.M., Ph.D.

The Division of Toxicology Research and Testing develops, validates, and evaluates methods for toxicity testing of chemicals and other environmental agents; is responsible for toxicity testing, using both short- and long-term bioassays, to determine or ascertain toxicity of chemicals and other environmental agents; coordinates and communicates test development and testing programs with other government agencies; and disseminates results of research, testing, methods development, and validation efforts to the scientific and public communities and to the regulatory agencies.

Ruth L. Kirschstein, M.D.

Director

Christine K. Carrico, Ph.D.

Director, Pharmacology Research Associate Program

Pharmacology Research Associates

The National Institute of General Medical Sciences (NIGMS) has 12 positions (medical staff fellow and staff fellow) available each year for pharmacology research training. The Pharmacology Research Associate Program seeks to develop leaders in pharmacological research for key positions in academic, industrial, and Federal research laboratories. It is intended for those who have made a commitment to pharmacology in their training or research, and for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in the field of pharmacology.

Those who are appointed begin on July 1 and receive 2 years of postdoctoral training in one of the participating laboratories of the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Fellows engage in research relating the principles of pharmacological sciences to contemporary biomedical problems. During their tenure, pharmacology research fellows devote the major portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities. A variety of laboratory problems and different research approaches advance both the work in progress and the competence of the prospective independent investigator.

Professional growth is stimulated through personal guidance by outstanding senior NIH and ADAMHA scientists who serve as preceptors. Preceptors and research fellows are matched by a mutual selection process after personal interviews.

Candidates for pharmacology research associate positions include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience or training in areas relevant to pharmacology. Those with research experience in a related area who wish to further their development in pharmacology are also eligible. Applicants with the M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related discipline.

Program Areas

The choice of a specific laboratory depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request any senior NIH or ADAMHA scientist as a preceptor. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. A description of these areas follows.

Clinical Pharmacology

Clinical pharmacology is an evolving research discipline that addresses the need for investigators to carry out pharmacological studies that relate to the mechanism(s) of action of clinically relevant drugs. An opportunity is available for 2 years of research training specifically in an area of clinical pharmacology. Applicants for this training should have the M.D. degree and a minimum of 1 year, preferably 2, of graduate medical training (internship or residency). This is a particularly good opportunity for M.D.s who have not had extensive independent laboratory experience but who are committed to obtaining such experience. For this reason, an intensive laboratory experience in at least one of the programs described in the next section constitutes 50 to 75 percent of the clinical pharmacology program. In order to prepare fellows either to relate laboratory methods to studies in humans or to carry out mechanistically oriented studies in humans, the program also includes training in such general clinical pharmacological principals as pharmacokinetics, pharmacodynamics, biostatistics, and drug evaluation.

In addition to the listed laboratory preceptors, investigators who are actively engaged in clinical pharmacological research in the Warren Grant Magnuson Clinical Center, NIH, are available to address fellows' special areas of need on an individual basis. These preceptors include but are not limited to:

James R. Gillette, Ph.D., Chief, Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute
Harry Keiser, M.D., Clinical Director, National Heart, Lung, and Blood Institute

Charles Myers, M.D., Chief, Clinical Pharmacology Branch,
National Cancer Institute
Daniel W. Nebert, M.D., Chief, Laboratory of Developmental
Pharmacology, National Institute of Child Health and Human
Development
Snorri S. Thorgeirsson, M.D., Ph.D., Chief, Laboratory of
Experimental Carcinogenesis, National Cancer Institute
Markku Linnoila, M.D., Ph.D., Chief, Laboratory of Clinical
Studies, National Institute on Alcohol Abuse and Alcoholism

William Z. Potter, M.D., Ph.D., intramural clinical
pharmacologist, serves as coordinator of each fellow's overall
training in clinical pharmacology. The clinical pharmacology
fellows' research experiences are planned individually to meet
the needs dictated by previous training, experience, and career
goals. This research experience can involve both laboratory
and human investigation.

A training plan, including formal coursework, is developed
for each fellow. A series of seminars are organized with the
participation of the clinical pharmacology fellows to ensure that
their needs are met.

An applicant may be considered for both the regular pharm-
acology research associate program and the clinical pharma-
cology option. Further information may be obtained from the
Pharmacology Research Associate Program, NIGMS, NIH,
Westwood Building, Room 919, Bethesda, Maryland 20892
(301/496-7707).

National Institute on Aging

Laboratory of Neurosciences—

Stanley I. Rapoport, M.D.

The basic and clinical research programs of the laboratory
cover several areas related to neuropharmacology and brain
disease: 1) blood-brain barrier transport (amino acids, divalent
ions, drugs) and modification of drugs to enhance their
transport; 2) cerebral glucose, protein, and lipid metabolism in
awake animals; 3) the pharmacokinetics and
pharmacodynamics of centrally acting drugs in animals and
humans, using analytical tools to determine drug metabolites;
4) gene expression in the central nervous system, using *in situ*
hybridization techniques, in relation to aging, plasticity, and
disease; 5) electrophysiology (patch and voltage clamping) and
pharmacology of cultured fetal neurons from normal and

trisomic mice, with regard to Down's syndrome; 6) the properties and distribution of neurochemical markers, including receptors, in postmortem brain tissue from healthy subjects and from patients with Alzheimer's disease; 7) positron emission tomography, using 18F-fluoro-2-deoxy-D-glucose to study brain metabolism and 15O-02 to study cerebral blood flow, in relation to human aging, Alzheimer's disease, Down's syndrome, and depression, and following drug stimulation of the central nervous system.

National Institute on Alcohol Abuse and Alcoholism

Unit for Special Projects Office of the Scientific Director— Boris Tabakoff, Ph.D.

This unit concentrates its efforts on problems related to the biochemical determinants of behavior and behavioral genetics. A selective breeding program for drug-induced neuroadaptation in rodents is under way. Neural mechanisms for development of tolerance to alcohol and other sedative hypnotics are being examined by molecular genetic, autoradiographic, and enzymatic techniques. Cell surface receptors for peptide hormones and immunologically active peptides are being examined, and the coupling of peptide recognition sites to intracellular events, such as generation of cyclic nucleotide and calcium homeostasis, is being studied.

Laboratory of Clinical Studies— Markku Linnoila, M.D., Ph.D.

This laboratory consists of a 10-bed research ward, 11 modules of laboratory space, and an animal facility in the NIH Clinical Center. There are five sections and three units in the laboratory. The major research interests consist of treatment and prevention of alcoholism and alcohol withdrawal. New medications with specific mechanisms of actions will be tried in detoxication and maintenance treatments of alcoholics. Both the pharmacokinetics and pharmacodynamics of the drugs are carefully monitored 24 hours a day with EEF, ECG, and BP telemetry as well as temperature and activity measurements. Cerebrospinal fluid, plasma and urine monoamines, and prostaglandins are quantified with mass fragmentography and liquid chromatography. Peptide neuromodulators are measured with radioimmunoassays after separation with chromatography.

Receptor functions are measured in blood cells and in animal experiments. Brain functioning is measured with electrophysiologic and imaging techniques over and beyond behavioral observations. Liver functioning will be characterized using C_{13} -labeled drugs as tools to evaluate metabolic rates of both flow- and enzyme-dependent drugs. Preclinical tests of drugs having potential for treatment of alcoholism will be conducted in the Clinical Brain Research Section of the laboratory. The Unit of Genetic Studies will use two-dimensional protein electrophoresis to detect protein polymorphisms in families with alcoholics and subsequently will engage in chromosomal mapping and genetic linkage analyses.

Laboratory of Physiologic and Pharmacologic Studies—
George Kunos, M.D., Ph.D.

This group is interested in the mechanisms of regulation of neurotransmitter receptors and central nervous system mechanisms of cardiovascular control. Specific areas of current research are: 1) the cellular mechanisms involved in the reciprocal, inverse regulation of alpha- and beta-adrenergic receptors in cultured liver cells, with special emphasis on the role of growth factors; 2) interactions between the immune and the autonomic nervous systems, as exemplified by the regulation of pulmonary beta-adrenergic receptors by interleukin-1 and related cytokines; and 3) interactions between catecholamines, opioid peptides, and amino acid neurotransmitters in the reflex regulation of blood pressure and in the cardiovascular effects of ethanol. These studies are pursued using a variety of biochemical, molecular biological, and neurophysiologic methods.

• Section on Receptor Mechanisms—
Paula L. Hoffman, Ph.D.

The research program in this section is primarily concerned with CNS mechanisms of ethanol tolerance and physical dependence. Projects include behavioral neurochemical and molecular biological analyses of systems influencing these phenomena. Neurotransmitter receptor-effector coupling processes, primarily those involving receptors linked to adenylate cyclase or to ion channels, are currently being investigated in brain and in tissue culture preparations. Basic mechanisms of receptor binding and receptor-effector coupling are investigated, as are the effects of acute and chronic ethanol

treatments on these processes. The section is also studying the role of arginine vasopressin in ethanol tolerance, including the localization and characterization of the CNS vasopressin receptors that mediate effects on tolerance, the neurochemical mechanisms of action of the peptide, and the effects of ethanol on the biosynthesis of vasopressin in brain. The investigations involve biochemical methodology, including receptor binding and enzyme assays, protein purification, and ion flux measurements. In addition, molecular biological techniques to assess mRNA and protein characteristics are used. Measurements of physiologic and behavioral responses to ethanol are also performed.

- Section on Immunology—
Randall L. Kincaid, Ph.D.

Studies in this section are concerned with the regulation of Ca^{2+} dependent signaling pathways in neural and lymphoid cells and their potential involvement in alcoholism and pathologies of the nervous and immune systems, such as AIDS. Research focuses on the interactions between cyclic nucleotide and phosphoprotein metabolism and their control by calcium and calmodulin. Ongoing studies of the phosphoprotein phosphatase calcineurin, recently cloned in this laboratory, emphasize modern molecular biological techniques. Long-term projects include the role of specific phosphoproteins in developmental/neuroadaptive processes and the relationship of cyclic nucleotide turnover to synaptic integration mechanisms.

- Section of Electrophysiology—
Forest F. Weight, M.D.

The Section of Electrophysiology conducts research on the physiology and pharmacology of neurons and synapses in the central and peripheral nervous systems. The general areas of investigation include: the regulation of nerve cell excitability and the release of neurotransmitter substance; the cellular actions of neurotransmitters such as acetylcholine, dopamine, serotonin, glutamate, and GABA; the membrane mechanisms of peptides such as enkephalin; and the interaction of various neuroactive substances such as ethanol, barbiturates, and opiates. Current research includes investigation of the molecular regulation of membrane ion channels. The research methods employed are primarily electrophysiologic, including

**National Institute of
Allergy and Infectious
Diseases**

intracellular recording, voltage-clamp, and patch-clamp techniques. In addition, optical recording methods are used to study the regulation of intracellular calcium ions.

Laboratory of Clinical Investigation—

Michael M. Frank, M.D.

The Laboratory of Clinical Investigation performs basic and clinical research on the pathophysiologic basis of disease in three general areas—allergy, clinical immunology, and infectious diseases. Ongoing investigations in allergy and immunology attempt to define the pathophysiologic basis of allergic disease in terms of the release of granular contents from mast cells; mucus secretion in the airways; control of blood flow to tissues involved in allergy, such as the nasal mucosa; excessive proliferation of cells involved in immediate hypersensitivity, as in mastocytosis; cellular function in host defense across mucosal barriers; and factors that control growth and differentiations of immune cells and factors that mediate and regulate the development of immune mechanism mediated tissue damage. Studies of structure and function of various cellular membrane receptors that control lymphocyte and phagocyte cell function are ongoing. Studies in infectious disease examine herpes virus pathophysiology; molecular biology and the use and function of antiviral agents; host defense against fungi and the role of antifungal agents; pathophysiologic responses of the phagocytic cell and the means by which it destroys invading organisms; and the role of antibody and complement in the production of immunologic damage and in host defense against parasitic, bacterial, fungal, and viral diseases. Studies include structure, function, and molecular biology of proteins important in the oxidative burst of phagocytes.

Drug-related studies have examined the effect of glucocorticoids on the trafficking of lymphocytes; the use of androgens in the treatment of immunologic disorders, including hereditary angioedema; new antiviral agents, including acyclovir, for the treatment of herpes genitalis; and new antifungal agents such as SF 86-327. Studies of new immunomodulatory agents are ongoing. Studies of drug action are conducted on a more basic level as well. For example, the laboratory has evaluated the usefulness of interferone gamma *in vivo* and *in vitro* in the management of granulocyte disorders.

Laboratory of Immunogenetics—

Thomas J. Kindt, Ph.D.

The principal focus of this laboratory is on the structure and regulatory interactions of cell-surface molecules encoded by the major histocompatibility complex (MHC) and other cell-surface molecules important in the functioning of the immune system. Using the methods of molecular biology, genes encoding relevant molecules are identified for study and cloned and sequenced as necessary. Studies are designed to determine the function of individual molecules, particularly those encoded within multigene families. Molecular interactions of cell-surface receptors with target complexes on other cells and with soluble factors that trigger, suppress, or modify immunologic reactivity are studied in the intact cell and in artificial environments constructed by transfection of isolated genes. Examples of current projects are: the role of DNA methylases and DNase hypersensitive sites in the regulation of immunoglobulin expression; tissue-specific and locus-specific regulation of class II MHC antigen expression in humans and rabbits; genetic control of T-cell receptor synthesis; and the role of T-cell receptor genes in disease susceptibility.

Laboratory of Immunoregulation— AIDS Clinical Study Section—

H. Clifford Lane, M.D.

This laboratory is involved in the basic research studies of human immune responses in normal and disease states and of the immunopathogenesis of HIV infection. The laboratory has an active clinical research program involved in studying and treating patients with AIDS and related diseases and in the phase I testing of candidate HIV vaccines. Clinical trials are currently under way involving both antiretroviral agents and immunomodulatory therapy, including bone marrow transplantation, interleukin-2, and interferon.

Note: The AIDS Clinical Study Section is the only part of the Laboratory of Immunoregulation that is open to PRAT fellows.

Laboratory of Viral Diseases—

Bernard Moss, M.D., Ph.D.

This is a molecular biology laboratory that carries out fundamental research on the structure of viruses, the replication and

expression of viral genomes, the interactions of viruses with host cells, and the factors associated with virulence in experimental animals. Genetic engineering is used to develop new approaches to the prevention and treatment of viral diseases. Determination of the mechanisms of action of antiviral agents and the construction of live recombinant vaccines and targeted therapeutics are additional areas of current investigation.

**National Institute of
Arthritis and
Musculoskeletal and
Skin Diseases**

Arthritis and Rheumatism Branch—

- Section on Chemical Immunology
Henry Metzger, M.D.

This section studies at the molecular level the structure and function of cell-membrane receptors. Using the receptor for immunoglobulin E of mast cells as a model, current efforts largely involve the use of molecular genetic and protein chemical techniques to analyze the mechanism of ligand binding and signal transduction.

Laboratory of Physical Biology—

Richard J. Podolsky, Ph.D.

This laboratory is concerned with the contraction and regulatory mechanisms in muscle cells. The primary goal is to gain an understanding of the molecular basis of force generation and shortening in muscle fibers. Present projects include one- and two-dimensional X-ray diffraction studies of intact and simplified muscle fiber preparations, correlation of filament structure derived from X-ray data with that obtained by electron microscopy, high time resolution mechanochemical studies, and radiation inactivation analysis of the physiologic function of various structural proteins.

Laboratory of Cellular Carcinogenesis and Tumor Promotion—

- Molecular Mechanisms of Tumor Promotion Section—
Peter M. Blumberg, Ph.D.

Tumor promoters are agents that, although not themselves carcinogenic, induce tumors in animals previously exposed to a sub-effective dose of a carcinogen. This section is studying the mechanism of action of the most potent class of tumor promoters for mouse skin, the phorbol esters, and has demonstrated that cells and tissues contain specific phorbol ester receptors. Characterization indicates that the major class of these receptors is identical to protein kinase C, to which the phorbol esters bind at a modulatory site. Diacylglycerol, an activator of protein kinase C, appears to be the endogenous analog of the phorbol esters, and the postulated normal role for the phorbol ester receptor/protein kinase C is to mediate responses to that large class of hormones and cellular effectors whose action is associated with phosphatidylinositol turnover rather than elevated cyclic AMP levels. Current research directions include clarifying the interaction of the receptor with membranes, determining the basis of receptor subclasses, defining the mechanism of coupling between phorbol ester binding and kinase activation, and tracing the pathways between substrate phosphorylation and subsequent biological response.

Laboratory of Experimental Therapeutics and Metabolism—

Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is analytical and clinical pharmacology involving studies on qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents using experimental systems, as well as in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued in collaboration with other NCI laboratories. The other major research area concerns the elucidation of fundamental chemicobiologic interactions underlying chemically-induced cytotoxicity and carcinogenicity to specific target organs and

target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic “activation” and “deactivation” systems are of interest, as are investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites in both normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemically-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimum toxicity to normal tissues.

Laboratory of Biological Chemistry—

Richard L. Cysyk, Ph.D.

This laboratory brings together scientists who identify, as targets for drug design, cellular reactions that are critical to tumor cell survival and to the control of cell division and differentiation. Emphasis is placed on targets uncovered by recent advances in cell biology. Compounds are designed to interfere with these targets and are evaluated for biochemical and antitumor effectiveness. Pharmacologic information—plasma levels, tissue levels, mechanisms of action, transport, and metabolism—is used for experimental chemotherapy and for preclinical evaluation of an agent. An important aspect of the selective toxicity of an agent is the effect of endogenous factors present *in vivo* that can modify the cytotoxic properties of the agent and thereby influence differential toxicity. This laboratory identifies and quantitates such endogenous factors, when possible, and devises methods to manipulate them to enhance the chemotherapeutic effectiveness of cytotoxic compounds.

Laboratory of Biological Chemistry—

Robert I. Glazer, Ph.D.

The research interests of this laboratory center on two major areas of investigation: 1) the role of the proto-oncogene tyrosine protein kinase, *c-fes*, in myeloid hematopoietic cell differentiation; and 2) characterization of the isoforms and proteolytic

activation of protein kinase C in multidrug-resistant leukemia and breast cancer cells. Both studies involve a variety of molecular biological and immunologic techniques such as cDNA and antisense RNA cloning, establishment of stably expressing cell lines via transfection, steady-state and transcriptional analysis of specific protein kinase mRNA's with antisense RNA probes, and characterization of protein kinases with sequence-specific antipeptide antibodies. The consequences of activation or inhibition of the *c-fes* tyrosine protein kinase and protein kinase C activities by various drugs are also examined by two-dimensional gel electrophoretic analysis of putative endogenous substrates in the various cell lines.

Laboratory of Human Carcinogenesis—

Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess: 1) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, 2) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation, and 3) host factors that determine differences in carcinogenic susceptibility among individuals. The two major areas of investigation are: *Molecular and Biochemical Epidemiology* focuses on measurement of gene polymorphism by molecular approaches (e.g., DNA polymorphism) to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogeninduced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens. *Molecular carcinogenesis* involves studies of the role of oncogenes and tumor suppressor genes in human cell carcinogenesis; phenotypic and genetic alterations during *in vitro* carcinogenesis; the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and extra-, inter-, and intracellular factors modulating growth and differentiation of human epithelial cells.

Laboratory of Tumor Virus Biology—

Peter M. Howley, M.D.

This laboratory engages in several areas of research to determine critical cellular and molecular factors involved in virus-associated transformation. Studies are designed to: 1) identify and characterize exogenous viruses associated with the initiation or progression of neoplasia in humans or in animals as models for human neoplasia; 2) elucidate the mechanisms by which viruses associated with naturally occurring carcinomas may induce or initiate neoplasia; 3) characterize and define the biology and molecular biology of viruses associated with naturally occurring carcinomas; 4) identify and characterize factors involved in viral and cellular gene regulation pertinent to carcinogenesis; and 5) elucidate and define the cellular and molecular basis of transformation and carcinogenic progression.

The major research effort of the laboratory is focused on the molecular biology of the papillomaviruses, including transcriptional regulation, transformation, plasmid replication, and carcinogenesis. The laboratory has also been involved in developing the papillomaviruses as mammalian cell cloning vectors and is interested in using these vectors to study regulated genes such as the human β -interferon gene and the rat preproinsulin gene. These studies are designed to determine the genetic sequences involved in proper gene regulation and to isolate cellular protein factors required for this regulation.

Laboratory of Biochemical Pharmacology—

David G. Johns, M.D., Ph.D.

This laboratory conducts an integrated program for the characterization of antitumor and antiretroviral (anti-AIDS) agents, implements basic research on mechanisms of antitumor and antiviral drug action and drug toxicity, and develops strategies for improving the clinical utility of new or existing anticancer and anti-AIDS drugs by overcoming resistance and/or by protection of normal tissues against toxicity. The effects of such agents are assessed in experimental model systems *in vitro* and *in vivo* and on a variety of potential subcellular sites (e.g., nucleic acids, nuclear proteins, microtubular proteins, enzyme systems). Analytical methodology is developed for *in vivo* studies with new agents and, where

warranted, biological studies with these agents are extended to the preclinical and Phase I (clinical pharmacology) stages. A wide range of methodologies is currently in use, including a variety of tissue culture techniques, assays of antiretroviral activity, instrumental analysis (HPLC, mass spectrometry, and NMR when required), affinity chromatography, DNA and RNA isolation and characterization hybridization, autoradiography, pharmacokinetic analysis, and enzyme characterization.

Clinical Pharmacology Branch—

Charles Myers, M.D.

This laboratory is involved in the identification and testing of antagonists to the known human growth factors. A major target is basic fibroblast growth factor. This growth factor is not only an important stimulus for tumor cell growth, but is also a major factor in tumor angiogenesis. Antagonists to platelet-derived growth factor and transforming growth factors alpha and beta are sought.

Laboratory of Molecular Biology—

Ira Pastan, M.D.

The laboratory is interested in developing targeted toxins for the treatment of human cancer and other diseases. *Pseudomonas* exotoxin (PE) has been coupled to monoclonal antibodies that react with human ovarian cancers. One of these conjugates currently is evaluated in women with ovarian cancer. New cytotoxic agents are created by fusing growth factor genes (IL-2, TGF, IL-6) to a modified PE gene to create chimeric toxins (IL-2-PE, TFG-PE, IL-6-PE) that only kill cells bearing specific receptors. Also, CD4 was fused to PE to create a molecule (CD4-PE) that kills HIV-infected cells. The mechanisms by which chimeric toxins enter and kill cells are studied by biochemical, genetic, and cell biological approaches in order to devise ways to improve the therapeutic efficacy of these agents.

• Molecular Cell Genetics Section—

Michael M. Gottesman, M.D.

This section develops tissue culture genetic models for the analysis of the mechanism(s) of drug resistance in human cancer cells. The scientists' work has emphasized the

establishment of human cell lines resistant to multiple drugs with the aim of understanding the molecular basis of this resistance. Genetic studies include dominance analysis using somatic cell hybrids and techniques of DNA-mediated gene transfer to clone mutant of amplified genes involved in the multiple-drug-resistance phenotype. Biochemical studies include use of monoclonal antibodies to study cell-surface alterations in resistant cells and studies on uptake of drugs by resistant cells. Other research focuses on the role of cyclic AMP in regulating cell growth and gene expression and the function of secreted acid proteases in tumor cells.

Metabolism Branch—

- Endocrinology Section—

James M. Phang, M.D.

This research program emphasizes the functions of metabolic intermediates as regulatory molecules and the modulation of these functions by hormones. Of special interest is pyrroline-5-carboxylate, the obligate intermediate in the interconversions of proline, ornithine, and glutamate. This molecule serves as a metabolic interlink between amino acids and ribonucleotides and participates in the early cellular events accompanying mitogenic activation by growth factors. Pyrroline-5-carboxylate also acts as an intercellular communicator. It is found in biological fluids such as plasma and aqueous humor and functions to transfer metabolic signals between cells and tissues.

Several approaches are used to elucidate the mechanisms of the pyrroline-5-carboxylate metabolic interlink and to demonstrate its physiologic significance. These include cellular physiology, biochemistry, molecular biology, and human physiology. This group is studying the processing of these signals to regulate ribonucleotide metabolism and gene expression. The investigators are also characterizing the enzymes of this regulatory system and planning to clone the genes coding for these enzymes. With the understanding of these mechanisms in normal and malignant cells, the scientists will seek specific pharmacologic approaches in order to manipulate pyrroline-5-carboxylate-mediated cellular response in normal and neoplastic cells.

Laboratory of Experimental Carcinogenesis—

Snorri S. Thorgeirsson, M.D., Ph.D.

This laboratory plans, develops, and implements a research program to elucidate mechanisms of malignant transformation in human and animal cells by chemical carcinogens and other cancer-causing agents; determines critical cellular and genetic factors involved in the initiation, promotion, and progression of these transformed cells; and, whenever possible, applies the knowledge obtained from these studies toward the effective prevention of cancer in humans. Studies are designed to: 1) identify and characterize exogenous and endogenous factors controlling the initiation, promotion, and progression of chemically-induced tumors; 2) elucidate the mechanisms underlying the regulation of gene expression and differentiation in both human and animal neoplasia; 3) define the mechanism by which modifiers of cellular differentiation may inhibit and/or promote the neoplastic process; and 4) characterize the metabolic processing and mutagenic potential of both known and suspected carcinogenic aromatic amines.

• Hormone Action and Oncogenesis Section—

Gordon L. Hager, Ph.D.

The laboratory studies the hormonal regulation of gene expression in eukaryotic cells and oncogenic transformation. Mechanisms of activation and repression of transcription by steroid hormones are under investigation, as well as the interplay between hormone induction pathways and tissue-specific expression.

The identification of transcription factors and studies on their mode of action is studied. Reconstruction of hormone induction and repression *in vitro* with nucleoprotein templates is the long-term goal. Studies with inducible promoters mobilized on BPV-based episomal replicons have shown that these elements are precisely and reproducibly organized at the chromatin level. The accurate reconstruction of regulation *in vitro* may require such specifically structured chromatin templates.

The laboratory also studies the development of retroviral-based vectors that permit the efficient transmission of genes into cells, in culture and in the animal, both for basic investigations and in medical applications. Particular emphasis is placed on vectors that allow regulated expression in the target cell.

Laboratory of Mathematical Biology—

- Theoretical Immunology Section—

John N. Weinstein, M.D., Ph.D.

The work of this group is focused on the clinical application of “targeted” biological agents in the context of cancer and AIDS. As it becomes feasible to tailor biologicals to order, the lack of information on their pharmacology, physiology, and biochemistry remains a major barrier to rational design. The group is taking a combined experimental/theoretical approach to the question, with current emphasis on monoclonal antibodies, antibody conjugates, and liposomes. A number of the *in vitro* and animal studies are closely correlated with clinical protocols in which some members of the group collaborate.

On the theoretical side, the group is constructing mathematical models of various aspects of the pharmacology and physiology of monoclonal antibodies. These analyses feed back to influence preclinical and clinical study design. The laboratory includes a supercomputer facility and has major strengths in molecular structure and molecular graphics. The group is developing physical-chemical algorithms for the analysis of ligand/receptor sequence data pertinent to antibodies and other biological agents.

National Institute of Child Health and Human Development

Endocrinology and Reproduction Research Branch—

Kevin J. Catt, M.D., Ph.D.

This branch conducts research into basic aspects of hormone action, with emphasis on the characterization and regulation of cell-surface receptors for peptide hormones and their associated membrane effector systems. Of particular interest are the receptor-mediated mechanisms involved in the regulation of pituitary, gonadal, and adrenal function. Current research includes studies on the receptors and mechanisms of action of hypothalamic and pituitary hormones, and on the control of steroid production in endocrine target cells of the gonads and adrenals. The role of hormones in cellular regulation is also examined in relation to normal and disordered human endocrine function, using *in vitro* systems for the analysis of hormone action and the stimulatory and inhibitory control of target-cell function. Specific areas of study include the role of neuropeptides in hypothalamic-pituitary regulation; the analysis of brain receptors for peptide hormones (angiotensin II,

GnRH, and CRF); the isolation of receptors for angiotensin, GnRH, and gonadotropins; the hormonal control of granulosa-cell differentiation and Leydig cell function; the renin-angiotensin system and aldosterone secretion; and the phosphorylation mechanisms involved in hormonal and metabolic regulation.

Office of the Scientific Director—

- Section on Growth Factors—

Gordon Guroff, Ph.D.

Investigators in this section are interested in the biochemical and physiologic actions of nerve growth factor. This factor has been studied for many years and its function is now clear: it is required for the development and survival of sympathetic and sensory neurons and for the development of portions of the central nervous system as well. Without nerve growth factor, sensory and sympathetic neurons die. The chemistry of nerve growth factor has been completely elucidated, but its mechanism of action, and indeed the mechanisms of action of the more than 30 other growth factors now known, are only dimly perceived.

This group's work involves a dissection of the biochemical events, particularly those in the nucleus, that follow the interaction of nerve growth factor with the cell. The systems used are organ cultures of sympathetic ganglia from neonatal animals and the PC12 cell, a pheochromocytoma clone that differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. In recent years, it has become clear that phosphorylative changes in the proteins of these cells are pivotal events in the actions of the factor. The laboratory is working to isolate and purify the proteins involved and the enzymes carrying out these phosphorylations, as well as to understand the role of these proteins in the structure and transcription of the DNA. The ultimate goal is to define the exact molecular mechanism of these peptide factors. Research is also in progress on the mechanism of signal transduction, the enzymology of neurite development, the expression of specific differentiation-related genes and the interactions of various growth factors in the development of cells.

Cell Biology and Metabolism Branch—

Richard D. Klausner, M.D.

This laboratory focuses on various areas of receptor and membrane biology. One program is aimed at understanding the molecular nature of the transcriptional control elements that determine the expression of the highly regulated human transferrin receptor. Basic techniques of recombinant DNA technology have been employed to clone the gene for this receptor and to analyze the sequences involved in the sensitivity of this gene to pharmacological agents that alter iron availability as well as to growth factors and the state of proliferation of the cell. This highly regulated receptor serves as a model for the molecular aspects of receptor regulation. Two groups are examining the role of specific receptors in the activation and proliferation of T cells. One is studying the structure and function of the murine T cell antigen receptor. This includes the identification, characterization, and purification of each of the six different chains of the receptor complex. Purification is permitting the sequencing of these proteins, which will allow the molecular cloning of the genes encoding the components of the receptor complex. The structure of the complex in different classes of T cells, during T cell development, and in abnormal T cells is being explored. The receptor undergoes a complex pattern of phosphorylation events upon ligand binding. The nature and function of these events are being dissected by structural and pharmacological approaches, and correlations between receptor phosphorylation, phospholipid turnover, calcium fluxes, and membrane potential are active areas of investigation. The interleukin-2 receptor drives T lymphocyte proliferation in response to the lymphokine IL-2. The gene encoding this receptor has been cloned and the promoter and regulatory regions are being characterized. Particular attention is being focused on understanding the expression of this gene in normal and leukemic T cells. The approaches in the laboratory include lipid and protein biochemistry, immunology, hybridoma technology, recombinant DNA technology, and cell biology.

Laboratory of Developmental Pharmacology—

Daniel W. Nebert, M.D.

This laboratory investigates gene expression, with special emphasis on enzymes that metabolize drugs, chemical carcinogens, and other environmental pollutants. Molecular genetic and recombinant DNA techniques are used to study differences in the expression of these genes among inbred mouse strains, as well as wild-type and variant cells in culture. Nucleotide and amino acid sequences, evolution, tissue and developmental specificity, the role of enhancer sequences, and *trans*-acting regulatory proteins such as inducer-receptor complexes are examined by means of expression vectors and shuttle vectors to learn about fundamental mechanisms involving drug metabolism induction, drug toxicity and teratogenesis, and chemical tumorigenesis and mutagenesis. One long-range goal is to develop recombinant DNA assays for predicting human populations at increased risk for certain types of environmentally induced toxicity, birth defects, and cancer.

Laboratory of Developmental Neurobiology—

Phillip G. Nelson, M.D., Ph.D.

Research in neurobiology is conducted using tissue cultures of normal and neoplastic nerve and muscle. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. The membrane mechanisms of action of some neuroactive peptides are under investigation. In addition, molecular genetic techniques are being applied to problems of nervous system development.

• Section on Neuroendocrinology—

David C. Klein, Ph.D.

Investigations in this section focus on the molecular mechanisms through which neuro-transmitters regulate gene expression, using cultured pinealocytes as the primary experimental model. There are three areas of activity. First, the adrenergic control of pineal cyclic AMP and cyclic GMP is studied; both cyclic nucleotides are regulated by α -adrenergic potentiation of β -adrenergic stimulation. Second, the role of membrane pro-

tein phosphorylation in transsynaptic signal transduction is investigated. And third, recombinant DNA techniques are being used to study how enzymes involved in the conversion of tryptophan to melatonin are regulated.

Laboratory of Theoretical and Physical Biology—

David Rodbard, M.D.

This laboratory studies receptors for hormones and neuro-peptides *in vitro*, and analyzes pharmacokinetic process *in vivo* using stable isotopes with liquid chromatography-mass spectrometry. The Section on Theoretical Biology studies drug-receptor interactions, combining experimental and computer-modeling approaches including computer-assisted optimization of experimental design. The multiple types and subtypes of the opiopeptide “sigma” and phencyclidine (PCP) receptor system are the present focus of attention.

The Section of Metabolic Analysis studies the metabolism of calcium, other metals, carbohydrates, steroids (cortisol, testosterone, vitamin D) and amino acids in humans to evaluate metabolic correlates of growth and development (e.g., effects of growth hormone, sex steroids, and pregnancy).

The Section on Macromolecular Analysis develops new methods for fractionation of proteins, polypeptides, viruses, and nucleic acids using electrophoretic and related physical-chemical methods.

Laboratory of Developmental Neurobiology—

- Section on Neuronal Secretory Systems—

James T. Russell, Ph.D.

This group studies the molecular and functional organization of the nerve terminal, using the hypothalamo-neurohypophyseal system as the model. The approaches employed include the biochemical pharmacology of secretion, molecular biology, and high-resolution image processing under video microscopy. The studies are aimed at the mechanisms of regulation of secretion by modulation of ionic channels (K^+ and Ca^{2+} channels) and by activation of receptors at the terminal (e.g., opiate receptors). Studies are under way to characterize a transient K^+ channel involved in control of action potential kinetics. Studies are also carried out with respect to the organization of the peptidergic secretory vesicle core, which

contains large concentrations of neuropeptides, and the vesicle membrane, which is essential in the cell biological processes of biosynthesis, storage, transport, and secretion of neuropeptides.

**National Institute of
Dental Research**

Neurobiology and Anesthesiology Branch—

Ronald Dubner, D.D.S., Ph.D.

This branch conducts studies on the neurobiological basis of somatic sensation, with emphasis on pain mechanisms. Neuropharmacological studies examine the effects of peripheral tissue and nerve damage on neurochemical mediators, utilizing radioimmunoassay techniques as well as immunocytochemical and molecular biological approaches. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns, utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Electrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavioral studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of opiates, monoamines, and other putative neurotransmitters in the brain on neural function and animal behavior are studied utilizing this behavioral model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacological agents utilized in the control of acute and chronic pain. Present studies include the role of endogenous opioid compounds in stress and analgesia, the mechanism of action and efficacy of tricyclic antidepressant drugs in the control of painful neuropathies, the efficacy of different opiate receptor agonists in the treatment of cancer pain, and the analgesic potency of nonsteroidal antiinflammatory drugs.

Laboratory of Developmental Biology and Anomalies—

George R. Martin, Ph.D.

This laboratory studies the synthesis and degradation of connective tissue and disorders and drugs that alter its normal structure and function. Mouse models of human diseases (such

as diabetes, cancer cell metastasis, oral-facial malformation, and brittle bone) are studied and also used as test systems to monitor potential therapeutic approaches. Differentiating cultured cells are used to detect and investigate the teratogenic action of drugs. Particular attention is directed toward genetic and environmental factors that alter the expression of connective tissue genes using recombinant DNA technology.

Laboratory of Oral Medicine—

Abner Louis Notkins, M.D.

The Laboratory of Oral Medicine conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (herpes simplex), with emphasis on recombinant DNA technology; the etiology and pathogenesis of leukoplakia and papillomas of the oral cavity; virus-induced immunopathology; the use of the transgenic mouse model to study the role of viral proteins in the pathogenesis of viral infections and autoimmune disorders; the role of interferon in autoimmune diseases; the etiology of various dermatologic disorders, including aphthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (Sjogren's syndrome and salivary gland tumors) and endocrine glands (diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various antiviral and anti-inflammatory agents in the treatment of oral lesions.

Laboratory of Microbiology and Immunology—

- Cellular Immunology Section

Sharon M. Wahl, Ph.D.

This section investigates basic mechanisms by which the host mobilizes and modulates cellular inflammatory reactions in defense against foreign antigens and infectious agents. Major efforts are directed at elucidating the gene expression, regulation, and function of the cytokines produced by lymphocytes and monocytes. The section is investigating the biological effects and biochemical characteristics of these immunoregulatory factors, which include interferon; interleukin-1, -2 and -3; tumor necrosis factor; transforming growth factor; colony

stimulating factors; prostaglandins; thromboxanes; and leukotrienes; and is defining their role in modulating the cellular inflammatory response.

Another priority of the section is to investigate the effects of viral infections, particularly HIV-1 and CMV, on cellular and humoral immune responses. Studies of inflammatory cells and mediators in disease states such as AIDS, rheumatoid arthritis, streptococcal cell wall-induced polyarthritis, granulomatous responses, endotoxic shock, and cystic fibrosis are directed at analyzing the pathogenic mechanisms of chronic inflammatory diseases. Modification of the natural history of these diseases by manipulation of the immune system using anti-inflammatory drugs, gamma-interferon, cyclosporin A, and antiviral drugs is an area of intense focus and clinical relevance.

**National Institute of
Diabetes and Digestive
and Kidney Diseases**

Genetics and Biochemistry Branch—

R. Daniel Camerini-Otero, M.D., Ph.D.

This laboratory studies the mechanisms of genetic recombination and gene conversion in mammalian cells, the regulation of gene expression in higher eukaryotes, and the biochemistry of nucleic acid-protein interactions. This group also conducts studies on the effects of physical and chemical agents on genetic recombination and DNA repair in mammalian cells. In several cases material from patients with genetic diseases is used to dissect the biochemical or molecular aspects of a problem under investigation. In order to carry out these studies the techniques utilized include molecular cloning, DNA sequencing, DNA-mediated gene transfer, construction of gene fusions and recombinant DNA libraries, and a variety of other biochemical and molecular techniques.

Laboratory of Molecular and Cellular Biology—

Barrie J. Carter, Ph.D.

This laboratory carries out fundamental research in the molecular biology of gene regulation of human viruses and cells, with special emphasis on the interaction of viral regulatory genes with cellular metabolism and the use of viruses as gene expression vectors. Major interacting areas of emphasis currently under investigation are: 1) the molecular biology of gene regulation in human parvoviruses; 2) studies of parvovirus-mediated inhibition of tumorigenesis by viral and

cellular oncogenes, inhibition of carcinogen-mediated gene amplification, and inhibition of tumor cell growth; 3) the development of viral transducing vectors for the stable integration and expression of genes; and 4) the development of novel antiviral therapies for HIV based on interference with the action of viral trans-regulatory genes.

Molecular, Cellular, and Nutritional Endocrinology Branch—

- Section on Experimental Diabetes, Metabolism and Nutrition—

Samuel W. Cushman, Ph.D.

Insulin's fundamental action to stimulate glucose transport has recently been shown to occur in the rat adipose cell model system through a rapid and reversible exocytic-/endocytic-like subcellular cycling of glucose transporters between a large intracellular pool and the plasma membrane. Insulin also stimulates the appearance of cell-surface insulin-like growth factor II (IGF-II) receptors and concomitantly induces insulin receptor internalization through similar rapid and reversible membrane translocation processes. Using biochemical, cell biological, and immunologic laboratory techniques, the section: 1) investigates the structure, function, and biosynthesis of integral membrane proteins involved in the hormonal regulation of carbohydrate and lipid metabolism, especially the receptors for insulin and IGF-II and the glucose transporter; 2) studies the molecular and cellular basis of hormone action, especially relating to the mechanism of insulin action and its counterregulation by catecholamines, other peptide hormones, and the glucocorticoids; and 3) examines the influence of altered metabolic and nutritional states on cellular function and its regulation by hormones, especially those states associated with perturbed insulin action such as diabetes, obesity, and altered dietary carbohydrate and fat intake.

- Section on Growth and Development—

Matthew M. Rechler, M.D.

The laboratory uses approaches of molecular and cellular biology to define the role in normal and pathological cell growth of a family of polypeptides, the insulin-like growth factors (IGF), present in plasma and chemically related to insulin. IGF receptors, actions, carrier proteins, and the

regulation of IGF gene expression are studied in appropriate model systems. The role of IGF-II in fetal growth and development, and in central nervous system function, are areas of current interest.

Laboratory of Bioorganic Chemistry—

- Section of Pharmacodynamics—

John W. Daly, Ph.D.

This section is engaged in research on the role of cyclic nucleotides and other second messengers in the nervous system, including: 1) the mechanisms of action of forskolin on adenylyl cyclase; 2) development of selective agonists/antagonists for receptors for catecholamines, adenosine, and other neuroregulators; 3) the relationship among membrane potential, ion flux, phospholipid turnover, and generation of cyclic nucleotides; 4) the interrelationship of sodium and calcium in the regulation of phosphoinositide, breakdown in action; and 5) the significance of protein kinases to second messenger formation and function of ion channels. The effects of new natural products and other agents on neuronal and muscular function are investigated with particular emphasis on using radioactive alkaloids such as batrachotoxin, histionicotoxin, and pumiliotoxin to investigate channels associated with transport and function of ions such as sodium, potassium, and calcium.

- Section of Oxidation Mechanisms—

Donald M. Jerina, Ph.D.

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrolase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrument techniques such as high pressure liquid chromatography, high resolution mass spectrometry-gas chromatography, and high-resolution magnetic resonance in the study of metabolism catalyzed by homogeneous cytochromes P-450, epoxide hydrolase, and the glutathione transferases.

Laboratory of Chemical Physics—

- Section of Macromolecular Biophysics—

William A. Eaton, M.D., Ph.D.

This section studies structure-function relationships in proteins using biophysical methods. A major interest is the investigation of hemoglobin S polymerization in purified solutions and in intact red blood cells. The overall aim of this research is to obtain a quantitative description of the pathophysiology of sickle-cell disease and to design strategies for developing a specific therapy. In addition to conventional biophysical methods, a number of special techniques are employed, including microspectrophotometry, laser photolysis, and light scattering for studying the kinetics and thermodynamics of polymerization in single red blood cells. Other projects in the section include the study of oxygen binding by normal hemoglobin using time-resolved absorption spectroscopy with nanosecond pulsed lasers and molecular dynamics calculations to stimulate the motions of the individual atoms during the binding process.

Laboratory of Molecular Biology—

- Section of Physical Chemistry—

Gary Felsenfeld, Ph.D.

This laboratory conducts research on the structure of DNA and chromatin within the eukaryotic nucleus, with particular emphasis on mechanisms of regulation of gene expression. Present studies are concerned with the isolation and characterization of specific factors that bind to the regulatory regions of genes that are being expressed, with the goals of identifying their roles in the control of expression and understanding in detail the molecular basis of that control. The laboratory also conducts physiochemical studies of DNA and its complexes with nuclear proteins. The methods used include standard techniques of molecular biology such as DNA cloning and sequencing, *Xenopus* oocyte injection, and *in vitro* transcriptional assays, as well as physiochemical methods applied to the determination of macromolecular structure and the measurement of the nature and strength of interactions between biologically important molecules.

Digestive Diseases Branch—

Jerry D. Gardner, M.D.

This laboratory investigates the cellular basis of action of gastrointestinal peptides using various isolated cell systems prepared from different gastrointestinal tissues. Gastrointestinal peptides being studied are cholecystokinin, secretin, VIP, PHI, bombesin, physalaemin, substance P, ranatensin, galanin, pancreatic polypeptide, and calcitonin gene-related peptide. Isolated cell systems have been prepared for gastric chief cells, gastric parietal cells, pancreatic acinar cells, gastrointestinal smooth muscle cells, small intestinal epithelial cells, colonic epithelial cells, hepatic parenchymal cells, and hepatic Kupfer cells. Studies of the cellular basis of action of a particular peptide include receptor identification; development of receptor-specific antagonists; exploration of the intracellular sequence of messenger action; and the relation among the final response, receptor occupation, and messenger variation.

Laboratory of Structural Biology—

Victor Ginsburg, Ph.D.

The research in this laboratory concerns the role of specific structures of eukaryotes and prokaryotes in disease. One section is concerned with the biology and immunology of complex carbohydrates. This work involves the use of monoclonal antibodies for the detection of carbohydrate antigens associated with cancer and cystic fibrosis as well as with development and differentiation. A second section is concerned with the role of the cell surface of Gram-negative bacteria in pathogenesis. This work involves the manipulation of pathogenic strains by molecular genetics and mutation in order to examine the interaction of cell-surface components with host internal defense systems, including specific antibodies, complement, and phagocytes.

Laboratory of Biochemistry and Metabolism—

William B. Jakoby, Ph.D.

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to their catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action of those enzymes catalyzing conjugation

reactions with glutathione or adding sulfate or methyl groups. Regulatory phenomena are examined at the molecular level. The esterases of rat liver are systematically characterized.

- Section on Enzymes and Cellular Biochemistry—
Enrico Cabib, Ph.D.

The main interest of this laboratory lies in the molecular mechanisms of morphogenesis in eukaryotic cells. As model systems, the primary septum and the cell wall of the yeast, *Saccharomyces cerevisiae*, are currently investigated. The approach consists of studying the biosynthesis of the main structural materials—chitin for the primary septum and β (1—3) glucan for the cell wall—at the enzymological, subcellular, and cellular levels. Since these materials impart shape to cell structures, it is expected that the information gathered in this way will give insights into the control and mechanism of shape formation. Techniques used include purification and kinetics of enzymes; isolation of subcellular structures, especially plasma membranes; electron microscopy; isolation of appropriate mutants; preparation of antibodies against polysaccharide synthetases; and cloning of the pertinent genes. Because of their potential use as antifungal agents, special attention is paid to inhibitors of the polysaccharide synthetases and to their mechanism of action.

Metabolic Diseases Branch—

- Mineral Metabolism Section—
Stephen Marx, M.D.

This laboratory investigates the actions of calcitropic hormones. The principal focus is on the mechanisms of action of v-ERB-A-related proteins, such as the receptors for vitamin D. Members of this superfamily of proteins function, at least in part, as ligand-dependent transcriptional enhancers. Studies are directed at understanding the rapid effects associated with receptor activation (i.e., the rise of cyclic GMP within 30 seconds), the subcellular organization and compartmentalization of the receptor, the interaction of the receptor with its targets and the consequences of mutations in the receptor gene. Methods used include immunohistochemistry, tissue culture and cell biology and molecular biology, including the development of efficient systems for receptor expression.

Laboratory of Cell Biology and Genetics—

- Section on Cell Biology and Biochemistry—
Harvey B. Pollard, M.D., Ph.D.

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells using techniques of molecular biology, electron microscopy, electrophysiology, cell biology, and biochemistry. The researchers are particularly interested in secretory processes in chromaffin cells, islets of Langerhans, platelets, and synaptosomes. Critical problems now under investigation include how secretory vesicle assembly is regulated, how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membranes, and how the subsequent release of vesicle contents during exocytosis occurs. The approach of this laboratory is to search for special proteins and processes that could mediate such events.

Clinical Endocrinology Branch—

Jacob Robbins, M.D.

The laboratory is engaged in studies related to the thyroid gland and thyroid hormones. The subjects of greatest interest have been thyroglobulin and related iodoproteins, the plasma transport proteins for thyroid hormones, the mechanism of entry of thyroid hormones into target cells, the metabolism of the hormones in tissues, and, on a clinical level, the management of thyroid neoplasms. In recent years, fellows have worked on the monodeiodination reaction responsible for the conversion of thyroxine to the active hormone, triiodothyronine, in liver cells; on energy-dependent transport of triiodothyronine and thyroxine into hepatocytes and into skeletal muscle, employing whole-organ and cultured-cell systems; and on the effect of lithium ion in slowing the release of thyroid iodine and lithium's use as an adjuvant in treating thyroid carcinoma with radioiodine. A current interest within the laboratory is to employ rat neuronal and glial cell lines to study the transport, metabolism, and actions of thyroid hormones in relation to myoblast differentiation.

- Section on Endocrine Biochemistry—

Jan Wolff, M.D., Ph.D.

The laboratory investigates cytoskeletal (especially microtubule) interactions with cell membrane function, particularly adenylate cyclase. This involves tubulin chemistry, regulation of microtubule polymerization by associated proteins, the monomer-dimer equilibrium and contact surface, calcium/calmodulin, and charge-charge effects, as well as the mechanism of action of antimicrotubule drugs. The laboratory is also studying regulation of membrane-bound and soluble adenylate cyclases by hormones, calmodulin, bacterial toxins, guanine nucleotide binding proteins including tubulin, and phospholipids. The goal is to understand the reciprocal regulation of these two components.

The laboratory is studying adenosine receptors and antagonists, the role of bacterial adenylate cyclases as virulence factors (along with toxins), their mechanism of activation, their method of entry into host cells, molecular changes required for entry, and possible cofactors involved in membrane penetration.

Diabetes Branch—

Jesse Roth, M.D.

Phillip Gorden, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially for insulin and insulin-like growth factors. Current projects are focused on the role of receptors and receptor antibodies in disease states, genetic disorders of the insulin receptor (including molecular biology of the receptor), biosynthesis of receptor components, the role of receptors in hormone action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects examine insulin and insulin receptors in the central nervous system; the evolutionary and embryologic origins of insulin, ACTH, somatostatin, and other peptide messenger molecules; and the role of such molecules in vertebrate embryos and in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

- Section on Molecular and Cellular Physiology—
Derek LeRoith, M.D., Ph.D.

The laboratory is investigating the regulation of the genes encoding insulin-like growth factor I (IGF-I) and the IGF-I receptor using current molecular biological techniques. The recent cloning of the pertinent cDNA's from rat tissues is under way. The expression of these genes in various models of altered growth, nutrition and diabetes is studied.

Sequence analysis of a number of splicing variants in IGF-I mRNA has revealed an unique form of translational regulation of IGF-I biosynthesis, and is studied using *in vitro* mutagenesis and *in vitro* and *in vivo* translational assays. More extensive characterization of this regulatory mechanism involve transfections of appropriate cell lines and RNA-binding protein assays. Structural studies of the IGF-I and IGF-I receptor genes are pursued to obtain further insights into the control of expression of these genes.

- Biochemistry and Molecular Pathophysiology Section—
Simeon Taylor, M.D., Ph.D.

This laboratory has two major research interests, both of which relate to the insulin receptor. The first area of interest involves investigation of the role of the receptor-associated protein kinase in mediating insulin action. The insulin receptor has two functional domains—an extracellular insulin binding site and an intracellular tyrosine-specific protein kinase activity. Recent data from other laboratories has emphasized the necessary role of the tyrosine kinase activity in mediating insulin action. This laboratory has identified an intracellular substrate for tyrosine phosphorylation by the insulin receptor. The scientists are presently characterizing this substrate in the hope of identifying its function and determining how that function is regulated by tyrosine-specific phosphorylation in response to insulin and other growth factors.

The second area of investigation focuses on the mechanism of insulin resistance in diabetic patients. This laboratory has identified a number of patients with genetic diseases associated with extreme resistance to the biological actions of insulin. Several of these patients have been shown to have abnormalities in the function of their insulin receptors. At present, the scientists are cloning cDNA and genomic DNA encoding the insulin receptors of these patients. This will enable the re-

searchers to identify mutations causing insulin-resistant diabetes in humans. In addition, the information obtained from these studies will be useful in suggesting further investigations into structure-function relationships of the insulin receptor protein as well as structure-function relationships of the regulatory regions of the insulin receptor gene.

Laboratory of Chemical Biology—

Alan N. Schechter, M.D.

The major interest of this laboratory is understanding the control of differentiation and development of human erythroid cells, using cell biological and molecular genetic methods to study the control of globin gene expression. Cloned globin genes, including control regions, are being transfected into erythroid and non-erythroid eukaryotic cells in order to understand the DNA sequence-specific and intracellular soluble factors that control the sequential expression of these genes. This work has as one of its long-range goals the possibility of treating human genetic diseases by transferring new genes into cells of patients. In addition to these basic studies, clinical protocols are under way to use noninvasive modalities (e.g., NMR imaging) to evaluate disease severity and response to therapy in sickle-cell patients and to use drugs (e.g., hydroxyurea) to activate fetal hemoglobin genes in patients with hemoglobinopathies.

Laboratory of Analytical Chemistry—

• Steroid Hormones Section—

S. Stoney Simons, Jr., Ph.D.

The objective of this group is to define, on a molecular level, the biological properties of the receptors for steroid hormones. Major efforts are devoted to studying the activities of glucocorticoid receptor-steroid complexes up to, and including, their effects on gene transcription. Current investigations concern the molecular details of steroid-receptor interactions, the nature of the biologically active nuclear binding site for receptor-steroid complexes, the mechanism of antiglucocorticoid action, and a novel modulation of glucocorticoid induction of specific genes. The experimental approaches include tissue culture, whole-cell bioassays, stable and transient transfection assays, gene

splicing, gel electrophoresis, nucleic acid hybridization, antibody-antigen interactions, affinity labeling, nuclear protein fractionation, and synthetic organic chemistry.

- Section on Biomedical Chemistry—

Paul F. Torrence, Ph.D.

Research in the section is currently directed toward understanding the chemistry and biochemistry of nucleosides, nucleotides, and oligonucleotides, especially as they relate to potential antiviral and/or antitumor agents. Of particular interest are the unusual oligonucleotides containing 2',5'-phosphodiester bonds; namely, 2-5A or 2'5'-oligo A. This molecule appears to be a mediator of certain antiviral effects of interferon and may also be involved in the regulation of cell proliferation. In an attempt to capitalize on this unique mechanism for chemotherapeutic purposes, this section pursues systematic studies of the relationship between oligonucleotide structure and the ability to bind to and activate 2-5A's target enzyme, a 2-5A-dependent endonuclease. Since 2-5A is a highly charged molecule and cannot penetrate the cell membrane, these studies also seek a 2-5A derivative that can cross the membrane efficiently. Toward these ends, 2'5'-oligo A analogs are prepared by organic chemical approaches and evaluated for these biological activities in several different cell-free assay systems. The delivery of nucleotides across lipophilic membranes is studied. Chemical delivery systems are sought that would temporarily mask the negative charge of such nucleotides and that could be used to obviate resistance to antitumor agents or to deliver nucleotides with anti-HIV activity across the blood-brain barrier to enhance their therapeutic effectiveness against AIDS.

Laboratory of Cellular and Developmental Biology—

Robert Simpson, M.D., Ph.D.

Chromatin structure and gene regulation is studied. Three areas are under active investigation. Studies at the molecular level of histone-DNA interactions in chromatin are carried out using *in vitro* mutagenesis to address the basis for nucleosome positioning; DNA constructs designed from such studies are used to investigate both the crystal structure of the chromatin core particle and higher-order chromatin structure. An *in vivo*

system for the analysis of chromatin structure of regulated genes has been developed using plasmid chromatin in yeast. Methods that allow purification, in biochemical amounts, of yeast chromatin containing regulated genes are under way. Scientists will isolate chromatin containing specific genes in the transcribed and repressed states and compare the composition and structure of the genome when the gene is turned on or off. Other areas of research involve comparisons of the chromatin structure of genes that are temporally (and in one case, spatially) regulated during early embryogenesis in sea urchins. The regulation of transcription of a set of histone genes and the gene for a collagen protein that is expressed in the mesenchyme lineage of the echinoderm embryo is studied. While taking a diverse approach to the regulation of transcription, the researchers employ similar methodology to address common questions in different systems.

Laboratory of Neuroscience—

- Section on Neurobiology—
Phil Skolnick, Ph.D.

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances that normally interact with these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical “whole animal” pharmacology. Specific projects currently under investigation include: 1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined “agonists” and “antagonists”; 2) identification of endogenous substances responsible for hepatic encephalopathy; 3) study of neurotransmitter-regulated ion channels; 4) defining the physiologic role of benzodiazepine receptors found outside the CNS; 5) the physiologic and pharmacological modulation of recognition sites and uptake systems in the CNS for psychoactive drugs (e.g., phenethylamines such as amphetamine) and the relationship of such sites to their functional role(s); and 6) neural regulation of immune function.

- **Section on Drug Design and Synthesis—**
Kenner C. Rice, Ph.D.

The primary focus of this program is the chemistry of drugs that affect the central nervous system, as it pertains to study of these agents and physiologic functions of their recognition sites. The narcotics and their antagonists, phencyclidine (PCP), benzodiazepines, and cannabinoids and serotanageric agents are of particular interest. Synthetic organic chemistry is a major and indispensable tool in the multidisciplinary approach utilized in these studies, which involve collaboration with biochemists; immunologists; and biochemical, neurochemical, and behavioral pharmacologists. An ongoing program aimed at the identification, purification, and elucidation of the structure and function of opiate receptor subpopulations in the overall modulation of the CNS requires the synthesis of new receptor ligands for several lines of investigation utilizing: 1) irreversible ligands specific for opiate receptor subpopulations; 2) high-specific-activity radiolabeled ligands for autoradiographic visualization of receptors; 3) conformationally restricted analogs of potent narcotics as topological probes; and 4) positron emission tomographic visualization of opiate receptor patterns in living brains. Similar studies of PCP recognition site(s), including efforts to identify a clinically useful antagonist PCP, are in progress. A more classical medicinal chemical program currently in progress involves application of the recently developed NIH Opiate Total Synthesis for synthesis of previously inaccessible unnatural enantiomers of important opium derivatives with the goal of identifying new pharmacological agents and effects of opiates not mediated through the stereospecific receptors.

Molecular Pathophysiology Branch—
Allen M. Spiegel, M.D.

A family of guanine nucleotide binding proteins (G proteins) transduces signals across membranes by coupling receptors to effector enzymes. Distinct G proteins couple: 1) receptors for hormones and neurotransmitters that stimulate or inhibit cAMP formation; 2) rhodopsin, a photon receptor, to a cGMP phosphodiesterase; 3) receptors for agonists that stimulate phosphatidylinositol turnover; and 4) receptors for agonists that modify ion channel function. The Molecular Pathophysiology

Branch studies the structure and function of G proteins. G proteins have been purified and used for the production of antibodies that have proved useful for studies of G protein structure, for immunocytochemical studies, for regional localization of G protein in brain, and for quantitation of G proteins as a function of cell differentiation. The laboratory studies states of altered target cell responsiveness for possible quantitative or qualitative changes in G proteins. Thus, a human genetic disorder characterized by generalized hormone resistance has been shown to result from a deficiency in the G protein linked to adenylate cyclase stimulation. The laboratory also searches for novel G proteins involved in membrane transduction. Such a protein has been identified in human neutrophils. Molecular biological approaches including genomic and cDNA cloning, expression and mutagenesis are employed to study G protein structure and function.

Laboratory of Biochemical Pharmacology—
Herbert Tabor, M.D.

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. These studies provide experience with a variety of techniques (enzyme characterization, bacteriophage methodology, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed on the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and yeast.

Other work in the laboratory includes studies on control mechanisms for other enzymes in bacteria and mammalian cell cultures, the mechanism of action of antibiotic agents, ribosome structure, bacterial permeability, protein structure, and RNA plasmid replication in yeast. Investigations are also carried out on developmental biology and organ regeneration in the rat and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

- Section on the Genetics of Simple Eukaryotes—
Reed B. Wickner, M.D.

Yeast has emerged as the primary model eukaryote for studies of molecular genetics. Many drugs have the same action on human cells and on yeast cells, but their mechanism of action can be more easily studied in yeast. This section is studying a group of RNA viruses of yeast. The scientists have found a cellular system that represses viral replication, and have identified a number of key cellular components on which viral replication depends. They have also developed *in vitro* viral replication systems for studying the mechanisms by which these components act. These findings could form the basis for the design and testing of antiviral drugs.

National Institute on Drug Abuse

(These laboratories are located in Baltimore, MD)

Laboratory of Molecular Pharmacology— Michael J. Kuhar, Ph.D.

This laboratory focuses on the molecular and anatomic mechanisms of action and effects of abused drugs. Major areas of investigation include research on drug receptors and related neurotransmitters and molecular genetics. Efforts to identify the receptor that mediates cocaine dependence and self-administration suggest that this receptor is the cocaine-binding site on the dopamine transporter. Attempts to characterize the transporter is under way. Other projects involve labeling receptors *in vivo* using positron emission tomography scanning in human subjects in attempts to clarify the involvement of specific neurotransmitter receptors in drug interaction and disease states. Receptor mapping by autoradiography is used. Projects in molecular genetics include: 1) identification of genes involved in the toxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); and 2) cloning genetic sequences for receptors.

Laboratory of Neuropharmacology— Edythe D. London, Ph.D.

The laboratory conducts studies designed to elucidate neurochemical and electrophysiologic mechanisms and anatomic circuits that mediate the behavioral and physiologic effects of abused drugs. A wide variety of approaches are used, including cerebral metabolic mapping in human volunteers and laboratory animals, receptor binding assays, purification

and identification of endogenous neuroactive substances, and electrophysiologic probes of neuronal circuits and single neurons. Positron emission tomography to allow the simultaneous measurement of drug effects on brain metabolism and on mood and feeling state is used. Ongoing experiments are directed at the development of new ligands for *in vivo* human studies of receptors as they relate to brain functional markers. Other studies address the interactions among various endogenous modulators (e.g., steroid hormones), drug and neurotransmitter receptors and electrophysiologic functional markers. A multidisciplinary approach is used in relating *in vitro* observations at several levels of organization to observations in whole animals.

National Institute of Environmental Health Sciences

This institute is the only one of the 13 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Molecular Biophysics—

Colin F. Chignell, Ph.D.

Research programs of the laboratory cover several areas, including the use of physiochemical techniques to monitor the interaction of chemical agents with biological systems; physical organic and bioorganic chemical studies of environmental agents, biological materials, and their conversion products; the development and application of mass spectrometry to the identification and quantitation of chemical agents and their metabolites in biological systems. The molecular biophysics program mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current projects include the generation of free-radical intermediates during the metabolism of xenobiotics and the mechanisms of chemically induced photosensitization (phototoxicity and photoallergy). In addition, NMR spectroscopy is being used to study the effects of environmental agents on metabolism and the biotransformation of chemical compounds *in vivo*. An important component of this program is an NMR imaging system that makes it possible to monitor the response of experimental animals to toxic chem-

icals. Other programs include the biochemistry of prostaglandins and leukotrienes (including the co-oxidation of carcinogens by prostaglandin synthetase and peroxidases); and the metabolic transformation of phthalate esters. The mass spectrometry laboratory is well equipped. Current research in this area includes the analysis of peptides and oligonucleotides by tandem mass spectrometry, the development of combined liquid chromatography-mass spectrometry for the analysis of environmental chemicals and their metabolites, and the application of tandem mass spectrometry to gas phase ion chemistry.

Laboratory of Reproductive and Developmental Toxicology—

- Developmental Endocrinology and Pharmacology Section—
John A. McLachlan, Ph.D.

Investigators in this section study the biology and chemistry of estrogens and estrogenic xenobiotics. A primary interest is the normal and abnormal influences of estrogens on target cell differentiation; permanently altered programs of cell differentiation include atypical expression of gene products and abnormal growth regulation. Studies routinely use fetal or immature mice, organ cultures of fetal target tissues, and primary cultures of epithelial or mesenchymal target cells. Cell cultures are used to determine the mechanisms of estrogen-induced neoplastic cell transformation. Areas of interest include genital tract pathobiology, hormone-associated growth factors, hormone-induced gene action, regulation of cell proliferation, estrogen receptors, structure-activity relationships of estrogenic chemicals, and target organ metabolism of estrogens.

- Reproductive Neuroendocrinology Section—
Andres Negro-Vilar, M.D., Ph.D.

Research in this section is directed toward understanding and defining the endocrine, paracrine, and autocrine roles of peptides and amines within the hypothalamic-pituitary-gonadal and adrenal axes. Several levels of integration are considered. At the subcellular level, the mechanisms involved in modulation of peptide hormone release are evaluated by analyzing activation of aminergic receptors, membrane phospholipid breakdown, calcium mobilization, and activation of other intracellular messenger systems, and correlating those events

with peptide hormone release. At the cellular level, potentiation or cooperation between peptides and amines to modify hormone release is also studied. *In vivo* studies include an analysis of the neurotransmitters and modulators that regulate or modify the pulsatile secretory pattern of different peptide hormones, definition of the role of opioid peptides in the regulation of pituitary and gonadal function, and investigation of the effects of stress or selected neurotoxins on central monoamine metabolism and in the secretion of pro-opiomelanocortin-derived peptides and other pituitary hormones.

Laboratory of Behavioral and Neurological Toxicology—
Clifford L. Mitchell, Ph.D.

The research programs of the laboratory are aimed at understanding neuronal plasticity and nervous system mechanisms responsible for adaptation to the environment. An interdisciplinary approach is taken, utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the role of opioid peptides and steroid hormones (especially glucocorticoids) in modulating limbic system activity. General approaches include the following: 1) investigations of the biophysical and molecular biological properties of excitable cells, 2) studies on afferent and feedback mechanisms that influence neuronal plasticity of selected functional systems, 3) studies on the neurobehavioral mechanisms involved in plasticity and adaptive responses to environmental agents, 4) studies on peptides and their effects on biological systems, 5) identification of vulnerable neural circuits by study of neurotransmitter translocations and enzyme analysis, and 6) studies on the fundamental roles of neurotransmitters or neuromodulators (such as brain peptides) in CNS adaptation following chemical or physical insult.

Laboratory of Pulmonary Pathobiology—
Paul Nettesheim, M.D.

The research programs of the Laboratory of Pulmonary Pathobiology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: 1) regulation of biosynthesis and

secretion of mucus glycoproteins; 2) metabolism of prostaglandins in the lungs and the effects of prostaglandins on some metabolic functions of the lung; 3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the noncellular alveolar lining layer disease; 4) the biology, life cycle, and function of respiratory tract epithelial cells studied with *in vivo* and *in vitro* techniques; 5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and 6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

Laboratory of Pharmacology—

- Molecular and Comparative Pharmacology Section—
Richard M. Philpot, Ph.D.

Research in this section is directed toward understanding the relationships between the metabolism of chemicals and cell-selective toxicity in liver and various extrahepatic tissues, particularly those of the lung. Biochemical (including molecular biology), chemical, immunochemical, pharmacological, and pharmacokinetic concepts are used to elucidate the mechanisms by which environmental contaminants exert their toxicological effects. An integrated experimental approach is often used in these studies (e.g., intact animals, isolated perfused organs, enriched populations of freshly isolated cells, cells in culture, subcellular fractions), although experiments are most frequently performed with purified enzymes (various isozymes of cytochrome P-450, glutathione S-transferase, and UDPGA-glucuronosyltransferase). Emphasis is currently being given to the characterization of isozymes of important xenobiotic-metabolizing enzymes found in lung tissue, their cellular distribution, their regulation, and their role in the biotransformation of both endogenous and exogenous chemicals.

Office of the Scientific Director—

- Membrane Transduction Section—
Martin Rodbell, Ph.D.

This section carries out research on the molecular basis for the action of hormones, neurotransmitters, and other biologic agents that act through cell membrane receptors. Such research covers the isolation and characterization of membrane components involved in signal transduction, including their ultrastructure, topography in membranes, and functions.

National Institute of Heart, Lung and Blood

Laboratory of Molecular Hematology—

W. French Anderson, M.D.

This laboratory studies the mechanism and regulation of mammalian gene expression, using hemoglobin biosynthesis and immunodeficiency as primary models. The major objective is to develop the understanding and techniques necessary to carry out gene therapy for human genetic diseases. Major areas of research include: gene cloning and gene transfer, retroviral vector development and isolation and characterization of *trans* factors involved in gene expression.

Laboratory of Kidney and Electrolyte Metabolism—

Maurice B. Burg, M.D.

This laboratory is studying renal tubule function, epithelial transport physiology and osmoregulation. Methods used include perfusion of isolated renal tubules, mathematical modeling, epithelial cell culture, quantitative light microscopy, electrophysiology, protein isolation, preparation of monoclonal antibodies and recombinant DNA.

Laboratory of Biochemistry—

- Section on Metabolic Regulation—
P. Boon Chock, Ph.D.

Investigators in this section carry out mechanistic studies on enzyme action and regulation using physical, chemical, immunologic and molecular biological methods. The purpose of the research is to gain fundamental knowledge on how key cellular events are regulated by metabolites. Emphasis is placed on roles of covalent modification in metabolic regulation and signal transduction, particularly those involving phosphorylation/dephosphorylation and ubiquitination/deubiquitination of

proteins/enzymes. Work on the regulation of glutamine synthetase and MgATP-dependent protein phosphatase reveals that the covalent modification/demodification cascade is a unique mechanism that provides signal amplification, rate amplification, flexibility, and enhanced sensitivity and is capable of integrating allosterism and differential rates of protein synthesis and degradation into cellular control.

Laboratory of Chemical Pharmacology—

James R. Gillette, Ph.D.

- **Section on Drug-Enzyme Interaction—**

James R. Gillette, Ph.D.

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the factors that govern the substrate specificity and product formation by isozymes of cytochrome P-450 in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal levels.

- **Section on Cellular Pharmacology—**

Michael A. Beaven, Ph.D.

This section studies drug and hormone action at the cellular level. Current work includes: studies on the mechanism of mast cell/basophil degranulation, particularly on the interrelationship of signals generated by Ca^{2+} fluxes and breakdown of inositol phospholipids; studies with other types of cultured cells to allow comparison of biochemical signals generated by hormone stimulation with those of antigen stimulation, and the study of cell-signaling mechanisms at the level of the membrane. The latter studies include research with permeabilized-cells, subcellular fractions, and protein components with the view to reconstituting responses with purified components to identify both stimulatory and modulatory pathways in cells.

- Section on Pharmacological Chemistry—
Lance R. Pohl, Pharm.D., Ph.D.

This section studies the metabolic and immunologic basis of drug-induced hypersensitivities (allergies) and the mechanism and biological consequences of the interaction of radical metabolites of xenobiotics and endogenous compounds with heme proteins such as cytochromes P-450, myoglobin and hemoglobin. The drug-induced hypersensitivity studies involve the isolation and characterization of drug-induced neoantigens and the investigation of their role in immunopathology. The products of the interaction of radical metabolites with heme proteins, which include soluble heme products and covalently bound heme-derived products, are characterized and their mechanisms of formation and pharmacological and toxicological activities are characterized. Each problem is approached utilizing modern techniques of chemistry, biochemistry, immunology, cellular biology and molecular biology.

Hypertension-Endocrine Branch—

- Section on Biochemical Pharmacology—
Ingeborg Hanbauer, Ph.D.

Several classes of organic compounds that inhibit the cellular Ca^{2+} influx through voltage-dependent Ca^{2+} channels have been developed for the treatment of cardiovascular diseases. The class of dihydropyridines has been found to be highly specific for the inhibition of the L-type Ca^{2+} channel, and radiolabeled compounds of this series were used in radioligand-binding studies that led to the isolation of binding proteins that were shown to be molecular components of the voltage-dependent Ca^{2+} channel.

Research carried out in this laboratory focuses on the regulation of voltage- and receptor-dependent ion channels located in neurons and/or myocardial cells. Radiolabeled dihydropyridines were used as biochemical probes to monitor the purification from brain tissue of an endogenous ligand that functions as a modulator of voltage-dependent Ca^{2+} channels in primary cultures of cerebellar granule cells or cortical neurons. The chemical structure of this modulator is presently being studied by mass spectrometric and amino acid sequencing techniques and its physiological functions are being characterized by patch-clamp studies carried out in neuroblastoma

cells and cardiac myocytes. Preliminary results show that this endogenous ligand specifically inhibits the L-type Ca^{2+} channel in neuronal cultures while the N- or T-type channels are not affected. Studies on the molecular mechanism involved in the interaction of the endogenous modulator with Ca^{2+} channels include measurements of $^{45}\text{Ca}^{2+}$ fluxes, activation of protein kinase C, steady-state levels of *C-fos* mRNA, and phosphorylation of specific membrane proteins.

In addition, pharmacological and biochemical aspects of the regulation of the Na^{+} -dependent cocaine binding sites that are linked to the dopamine transport system are being studied in striatal dopaminergic nerve terminals or in cultured mesencephalic neurons.

Laboratory of Cell Biology—

Edward D. Korn, Ph.D.

This laboratory's research is concerned with the regulation of the polymerization and enzymatic activity of actin and myosin, the two major cytoskeletal proteins of the membrane-cytoskeleton complex on non-muscle cells. The investigators are studying the ways in which ATP hydrolysis regulates actin polymerization and how myosin phosphorylation regulates myosin polymerization, actomyosin ATP-ase activity, and contractile activity. These studies include active site sequence determination and structure-function relationships studied through a variety of protein physical-chemical methods. Other research involves isolating and sequencing myosin genes, with plans to undertake site-directed mutagenesis to explore further the chemical basis of actin and myosin function. Also under investigation is the action of drugs such as cytochalasin D in order to understand at the molecular level their effects on the membrane-cytoskeleton complex.

Laboratory of Biochemical Genetics—

Marshall W. Nirenberg, Ph.D.

- **Section on Molecular Biology—**

Marshall W. Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry, particularly those that pertain to the development of the nervous system, are studied in this section. Current research is focused on elucidating mechanisms that regulate gene

expression using recombinant DNA techniques. Polyclonal and monoclonal antibodies are being used to detect protein whose expression is dependent on cloned DNA. Cultured cells are used in many studies. Research also is being conducted on cyclic nucleotides, receptors, and ion channels.

- Section on Macromolecules—

Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms in *Escherichia coli*. One area of interest concerns the control of the synthesis and metabolism of cyclic AMP in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells. The laboratory is using biochemical and recombinant DNA approaches to study the regulation of expression of the gene for adenylate cyclase as well as the factors that regulate the enzyme's activity. Another focus of attention is the *Escherichia coli* cyclic AMP receptor protein. Analyses of structure, function, and repression mechanisms involving this protein are under way.

Laboratory of Cellular Metabolism—

Martha Vaughan, M.D.

This laboratory uses techniques of molecular genetics, biochemistry, and cell biology to study mechanisms of transmembrane signaling by guanyl nucleotide-binding (G) proteins, which regulate many critical cellular processes. Cyclic AMP synthesis by adenylate cyclase is controlled by stimulatory and inhibitory agonists (e.g., hormones, neurotransmitters) acting through cell-surface receptors. Signals generated by receptor-agonist interaction are transmitted to the catalytic unit via G proteins, which are targets for covalent modification (ADP ribosylation) catalyzed by bacterial toxins (e.g., cholera toxin, pertussis toxin) that alter their activity. G proteins are also involved in receptor-mediated regulation of phospholipid metabolism (e.g., inositol phosphate and prostaglandin production), ion flux, and cyclic nucleotide degradation. Areas of current interest include: 1) molecular biology: isolation of cDNAs and genes for G proteins, analysis of G protein mRNAs and alternative splicing mechanisms in diverse tissues and

differentiating systems, and *in vitro* mutagenesis with expression in cultured cells and *E. coli*; 2) membrane biochemistry: molecular mechanisms of interaction of adenylate cyclase components probed with sitespecific monoclonal antibodies, reconstitution of purified proteins and toxin-catalyzed ADP ribosylation to modify G protein function; 3) cell biology: effects of hormones and toxins on cyclic nucleotide content and arachidonate metabolism and cultured cells; and 4) protein chemistry: identification of enzymes and substrates of the ADP ribosylation cycle in animal cells, effects of ADP ribosylation on enzyme function; and regulatory properties of the phosphodiesterases that degrade cyclic nucleotides.

- Section on Biochemical Physiology—

Vincent C. Manganiello, M.D., Ph.D.

Research focuses on the isolation, purification, characterization and regulatory properties of specific cyclic nucleotide phosphodiesterases, and on the importance of these enzymes in the regulation of cyclic nucleotide-mediated processes and hormone action, especially that of insulin. Multiple types of phosphodiesterases are present in mammalian cells; drugs and specific inhibitors and effectors have served as useful tools in identifying distinct functional types of phosphodiesterases. One specific membrane-associated cAMP phosphodiesterase has been purified from adipose tissue; activation of this phosphodiesterase in intact adipocytes seems to be important in the antilipolytic action of insulin. A similar type of cAMP phosphodiesterase has been characterized in ventricular muscle and in platelets, where it seems to be a relatively specific intracellular site of action for several classes of recently developed therapeutic agents, and has been implicated in the regulation of myocardial contractility and platelet aggregation. Pharmacological, biochemical, immunologic, cellular biological and molecular genetic approaches are utilized to understand the mechanisms whereby insulin and other hormones and effectors regulate the membrane-associated cAMP phosphodiesterase in adipocytes. This information will be utilized to detect and define certain pathologic states and eventually to design appropriate therapeutic measures.

Other projects of interest include characterization of the allosteric and catalytic properties of the cGMP-stimulated phosphodiesterase and comparison of cyclic nucleotide

binding domains on this and other phosphodiesterases, including the rod outer segment cGMP phosphodiesterase; study of the characteristics and function roles of specific phosphodiesterases in circulating cells (the cGMP-inhibited form in platelets and the RO 20-1724 inhibited form in leukocytes); and study of the characteristics and function roles of the cGMP-stimulated and RO 20-1724-inhibited phosphodiesterases in the brain.

National Institute of Mental Health

Laboratory of Cell Biology—

Michael J. Brownstein, M.D., Ph.D.

The members of this group want to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, they want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products. The investigators hope to show how these processes are regulated by hormones and neurotransmitters at the transcriptional, translational, and post-translational levels. Finally, they are engaged in characterizing neurotransmitter receptors in order to determine more about the molecular basis of signal transduction.

- **Section on Pharmacology—**

Julius Axelrod, Ph.D.

Michael J. Brownstein, M.D., Ph.D.

This section studies biochemical pharmacology. These include studies on the development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of hormone and neurotransmitter secretion, methylation reactions and signal transduction mechanisms.

- **Section on Biochemical Pharmacology—**

Martin Zatz, M.D., Ph.D.

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated by light and neurotransmitters. The other concerns the effects of lithium on membrane functions. Related topics include brain inositol and cyclic nucleotide metabolism, Vitamin A and photoreception, and the pineal gland.

Biochemical and pharmacologic approaches to these problems are emphasized.

Laboratory of Cerebral Metabolism—

- Section on Clinical Brain Imaging—
Chuang C. Chiueh, Ph.D.

The members of this group engage in designing and characterizing *in vivo* ligands for imaging neurotransmitters and their uptake, receptors, or biosynthetic enzyme binding sites. The research and development of these neuroimaging ligands may lead to future clinical brain imaging procedures for studying up- and down-regulation of the turnover rate of neurotransmitters and their receptors in living patients suffering from neurological and/or mental disorders. The major focus of the present research is on the use of the MPTP-induced monkey model of parkinsonism for characterization of a newly developed presynaptic position emission tomography imaging ligand, 6-¹⁸F-DOPA, in determining brain injury and the turnover rate of striatal dopamine. The aging or neurotoxin induced up-regulation of supersensitive D-2 dopamine receptors is currently under investigation using a newly designed 3-¹²³I-benzamide, *ex vivo* autoradiography, and *in vivo* SPECT (single photon emission computerized tomography) brain imaging procedure. Other research interests involve characterizing and defining basic neurochemical, neuropharmacological, and neurotoxic mechanisms of MPTP, cocaine, amphetamine, neuroleptics, deprenyl, and new agents used in promoting sprouting or in retarding a progressive degenerative process of the pigmented A-9 dopamine neurons.

- Section on Developmental Neurochemistry—
Louis Sokoloff, M.D.

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the local rates of glucose consumption within the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pharmacological states. Methods for the

measurement of other biochemical processes such as protein synthesis, in localized regions of the brain *in vivo*, are under development and applied to neurobiological problems.

Laboratory of Neurochemistry—

Seymour Kaufman, Ph.D.

The main effort of this laboratory is devoted to studies of the regulation of the synthesis of the biogenic amine neurotransmitters dopamine, norepinephrine, and serotonin. Current research involves the molecular characterization of the phenylalanine, tyrosine, and tryptophan hydroxylases—the enzymes that catalyze the rate-limiting steps in the biosynthesis of these neurotransmitters—as well as the enzymes involved in the biosynthesis of the coenzymes that is essential for these reactions, tetrahydrobiopterin. The researchers are studying the regulation of these enzymes by hormones, drugs, membrane depolarization and diet, using techniques such as HPLC and affinity chromatography and tools such as monoclonal antibodies. Also being investigated is the regulation of the activity of these enzymes with the aid of recombinant DNA technology and genetically engineered proteins.

Laboratory of Molecular Biology—

- Section on Regulatory Proteins—

Werner A. Klee, Ph.D.

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that normally interact with the opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase complexes, including especially GTP binding and hydrolyzing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

- Section on Biophysical Chemistry—

David M. Neville, Jr., M.D.

This section studies the mechanisms of action of protein toxins such as ricin, diphtheria, and tetanus toxin. Particular emphasis is given to the receptor-mediated entry processes to the cytosol compartment. These pathologic processes are viewed as analogous to physiologic protein and peptide transport thought to be involved in signaling events. In conjunction with the basic program the section designs, synthesizes, and tests monoclonal antibody-toxin conjugates (immunotoxins) for use as therapeutic reagents in eliminating unwanted cell types from mixed-cell populations. Current goals are to increase the therapeutic ratio of immunotoxins to permit *in vivo* use. Design consideration will utilize newly acquired knowledge on toxin entry mechanisms. Active collaborations with clinical groups are maintained.

Clinical Neuroscience Branch—

- Unit on Behavioral Neuropharmacology—

Jacqueline N. Crawley, Ph.D.

The laboratory focuses on animal models relevant to psychopathologies such as schizophrenia, Alzheimer's disease, anxiety and depression. Simple rodent behaviors are employed to study neurochemical events mediating behavioral states. The functional significance of the neuropeptides recently discovered in high concentrations in mammalian brain pathways mediating emotional behaviors is studied. Neuropeptides such as cholecystokinin and galanin, which coexist with neurotransmitters such as dopamine and acetylcholine that have been implicated in schizophrenia and memory disorders, are also studied. Approaches used in the laboratory include micro-injection of peptides into brain nuclei; quantitation of simple, naturalistic rodent behaviors; microdialysis sampling and assaying of *in vivo* neurotransmitter release; receptor binding assays; and *in situ* hybridization of messenger RNA for the synthetic enzymes and receptors of neurotransmitters.

- Molecular Neurogenetics Unit—

Edward Ginns, M.D., Ph.D.

The research in this unit is part of an effort to understand better the molecular mechanisms underlying human nervous system development and function, as well as the pathogenesis

of certain neurological and psychiatric diseases. The group's clinical investigation of neurogenetic disorders is closely linked to its basic research programs for the development of techniques for improved diagnosis and recombinant DNA strategies for therapy. In particular, the unit's studies focus on lysosomal storage disorders, bipolar affective illness, schizophrenia, and related neurogenetic diseases. The scientists are describing the structural and active site properties of lysosomal hydrolases, nervous system proteins (particularly those that interact with pharmacological agents, excitable membranes, and/or receptors), and venom toxins. The cell-specific and developmentally regulated expression of proteins within the nervous system is investigated using the neuron-specific and non-neuronal enolase isozymes as a model. The genomic organization and regulation of expression of genes are studied. Therapeutic approaches for selected inherited disorders (such as Gaucher disease and Fabry's disease) utilizing retroviral-mediated somatic cell gene transfer are being examined using both *in vitro* cell culture and bone marrow transplantation.

- Section on Preclinical Studies—
- Section on Molecular Pharmacology—
Steven M. Paul, M.D.

The major research interests of these sections involve characterizing and defining the basic genetic, neurochemical, and electrophysiologic mechanisms of synaptic transmission, as well as the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with these mechanisms. Many studies involve characterization of neurotransmitter and drug receptors and recognition sites, characterization of ion channels, and definition of the relevant interactions of psychotropic drugs with these membrane proteins. Several receptor-effector systems and drug recognition sites are currently under investigation, including receptors for benzodiazepines/GABA, tricyclic antidepressants, psychomotor stimulants (amphetamine, methylphenidate), acetylcholine, serotonin, adenosine, and various neuropeptides (e.g., cholecystokinin). The role and regulation of these systems are investigated by 1) biochemical and pharmacological characterization of the recognition sites (including purification of receptor protein using affinity chromatography), defining receptor subunity by gel electrophoresis and radiation

inactivation, and the production of selective monoclonal antibodies to define functional receptor domains labeled by various radioligands; 2) molecular biological studies on the transcriptional and translational control of receptor/channel protein, especially as they apply to acute and chronic changes in drug sensitivity (tolerance/dependence); 3) development of appropriate *in vitro* models for studying these receptor-effector systems (brain slices, tissue culture); 4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; 5) behavioral and pharmacological experiments in animals; 6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor-effector changes in correlation with the behavioral manifestations of these genetic mutations; 7) post-receptor events, including calcium transport, cyclic nucleotide changes, and agonist-induced phosphatidylinositol hydrolysis; and 8) electrophysiologic experiments using single-unit recording techniques which are integrated with the biochemical studies in an attempt to relate these findings to physiologic changes in neuronal excitability.

- Section on Brain Biochemistry—

Steven M. Paul, M.D.

Neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell-surface receptor. This section uses radiolabeled ligands with fully preserved biological activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain tissue in which neuroanatomical relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus, with emphasis on identifying opiateergic neurocircuitry systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g., angeldustin, bombesin, substance P, neurotensin, CCK) are studied. The characterization, measurement, visualization, and

solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally, is studied.

Laboratory of Clinical Science—

- Section on Analytical Biochemistry—
Sanford P. Markey, Ph.D.

The focus of research in this section is on determining mechanisms underlying neuropathologic processes using newer physical methods of measurement. In current studies, the metabolism and action of the parkinsonian syndrome-producing neurotoxin MPTP and MPTP analogs synthesized in the laboratory are being studied. Several state-of-the-art mass spectrometers are used to qualitatively identify and quantitatively evaluate neurotoxin metabolism and its effects on various neurotransmitters. Antibodies to MPTP and its major brain metabolite, MPP⁺, are being used to assess the possible contribution of structurally similar agents to idiopathic Parkinson's disease. Detection of antibody cross-reactivity or toxicity of extracts toward dopaminergic cells in culture will be followed by isolation and structure elucidation of the naturally occurring neurotoxins. Two other neurotoxins, quinolinic acid, and intermediary metabolite of tryptophan, and the amino acid BMAA, which is isolated from cycad, are under investigation using mass spectrometric techniques for quantification and metabolism studies. Instrumental studies using tandem mass spectrometry, continuous fast atom bombardment, and laser desorption-Fourier transform mass spectrometry are in progress in order to extend the range of substances and types of processes that pharmacologists can analyze directly.

- Section on Pharmacology—
Juan M. Saavedra, M.D.

This section's research program focuses on three areas: the central mechanisms involved in the control of pituitary function and sympathetic activity, the localization and characterization of brain neuropeptide and amine receptors by quantitative autoradiography, and the regulation of the immune system by sympathetic nerves and hormones. The scientists use a combination of microanalytical techniques, radioenzymatic assays, radioimmunoassays, high pressure liquid chromatography, and

molecular biology techniques to study the metabolism of biogenic amines and neuropeptides in selected brain areas of several experimental and genetic animal models. The section is also interested in the utilization and development of image analysis techniques with computerized microdensitometry for autoradiographic quantitation and characterization of receptors for neuropeptides and biogenic amines, enzymes, and other antigens in single nuclei of rat and human brain and in the combination of autoradiographic methods and molecular biology techniques.

- Section on Histopharmacology—

David M. Jacobowitz, Ph.D.

This group is in search of unusual proteins in the brain and other areas of the body that will allow the generation of antisera that can be used as immunologic probes in order to reveal neuronal circuitry, cell classes, and other interesting structures in the brain and periphery. Two-dimensional gel electrophoresis and column chromatography are being used for the isolation and purification of brain proteins. Immunocytochemical methods are used to study the brain. Cell cultures are used to study proteins within astrocytes, microglia, and endothelial cells of the brain. *In situ*, hybridization histochemistry is used to identify mRNA of brain neuropeptides and proteins.

Biological Psychiatry Branch—

Robert M. Post, M.D.

This laboratory is engaged in studies of the clinical and behavioral pharmacology of various psychotropic drugs, particularly antidepressants, antipsychotics, anxiolytics, and anticonvulsants. The anticonvulsant carbamazepine has recently been found to have acute and prophylactic effects in both phases of manic-depressive illness. Studies are aimed at elucidating the possible mechanisms of action of this drug in seizure and affective disorders based on studies of clinical populations and laboratory animals.

Investigators work in a multidisciplinary laboratory environment where active interchange among clinicians and basic scientists is encouraged. The laboratory component (which could form the entire fellowship experience or be integrated with a clinical phase) could also involve studies of

the behavioral pharmacology of chronic psychomotor stimulant administration and the neural mechanisms underlying long-term behavioral and physiological changes observed in electro-physiological kindling. Techniques of clinical pharmacology, biochemistry, and behavioral analysis, with a particular focus on the roles of conditioning and learning mechanisms in longterm changes in behavior, would be emphasized. The fellows would be able to learn techniques of behavioral pharmacology, animal modeling, biochemistry, and physiology based on *in vivo* and tissue-slice preparations, and would study the biochemistry of classical neurotransmitters and peptides and their receptors using a variety of techniques, including receptor autoradiography. The fellowship would involve intensive individual work on one or more projects that would be designed, conducted, presented, and written up for publication by the fellow under the supervision and tutelage of the preceptor and senior colleagues in the laboratory.

- Biological Psychiatry Branch—

Agu Pert, Ph.D.

This laboratory is concerned with studying the functional activity of specific neuronal systems in the brain during various physiologic, behavioral, and pharmacological states. Two *in vivo* autoradiographic procedures are presently used to assess functional brain activity. The first is based on the assumption that enhanced activity of specific neurohumoral systems in the brain will increase the release of endogenous ligands, which will in turn compete with systemically administered radio-labeled ligands for binding at specific receptor sites. This *in vivo* autoradiographic procedure has already been applied successfully to study the functional activity of endogenous opioid systems during stress, pain, brain stimulation, and sexual behavior using ^3H -diprenorphine as the exogenous ligand. The second procedure involves the use of 2-deoxyglucose to study regional cerebral metabolism during various behavioral and pharmacological manipulations. In addition to *in vivo* autoradiographic analyses, the laboratory is also studying the distribution of peptide and neurotransmitter receptors in the brain using *in vitro* autoradiographic procedures and analyzing the functional effects of peptides on behavior using microinjection techniques.

Laboratory of Preclinical Pharmacology—

- Section on Neuropeptides—

Hsiu-Ying T. Yang, Ph.D.

This section is concerned with research on the neuropeptides in the brain and peripheral nervous system. Current studies are on the physiologic role of FMRF-NH₂-like peptides (putative endogenous antiopeptide peptides) in the mammalian CNS. The emphasis of the study is to investigate the possible role of FMRF-NH₂-like peptides in the development of opioid tolerance. The role of Neuropeptide Y (NPY) in adrenal function, especially the interaction of NPY with catecholamines in adrenal function, is investigated.

- Group on Receptor Pharmacology—

De-Maw Chuang, Ph.D.

This group conducts research in several areas related to molecular neuropharmacology. These include studies on: 1) molecular events of internalization of β -adrenergic receptors in cells desensitized with β -adrenergic agonists; 2) mechanisms of action of antidepressant drugs with emphasis on the physiological and pharmacological roles of high-affinity recognition sites for these drugs; and 3) regulation by neurotransmitters and neuromodulators of phospholipid metabolism by phospholipases C and A2 in primary cultures of neurons, cultured tumor cells, rat aorta, and brain slices. This laboratory also uses hybridoma and cDNA techniques to quantitate mRNA levels for neurotransmitter receptors.

National Institute of Neurological Disorders and Stroke

Laboratory of Neurophysiology—

Jeffery L. Barker, M.D., and

Thomas G. Smith, Jr., M.D.

The principal aim of this laboratory is a multidisciplinary analysis of the cellular properties of specific CNS neurons and the pharmacological effects of clinically important drugs on these properties. Most of the research is conducted using monolayer cultures of neurons dissociated from different regions of the embryonic CNS. The methods employed are primarily electrophysiologic, including intracellular recording, voltage-clamp, and patch-clamp techniques, although other methods, including biochemical and morphologic approaches, are also utilized. Specific projects include the comparison of chemically and electrically excitable membrane properties in

CNS neurons and the effects of clinically important drugs on these properties, the identification of specific cell types using immunohistochemical and biochemical methods, and the separation of specific populations of neurons using fluorescence-activated cell-sorting techniques.

Experimental Therapeutics Branch—

- Pharmacology Section—

Thomas N. Chase, M.D.

Clinical and preclinical studies are directed toward the development of improved therapies for dementing and extrapyramidal diseases. Transmitter pharmacology strategies concentrate on the dopamine system and closely interactive peptidergic pathways. Information from positron emission tomography allows the localization and biochemical characterization of brain transmitters. These findings give rise to pathogenetic hypotheses, linking an abnormality in a specific transmitter system with the presence of a particular neurological sign. Following evaluation in various animal models as well as in patients using selective pharmaceutical probes, hypotheses motivate the design of novel pharmaceutical interventions. Current preclinical projects include biochemical and behavioral studies of various animal models of Alzheimer's and Parkinson's disease and an examination of the effects of selective D-1 or D-2 dopamine agonists and antagonists on motor behavior. Ongoing clinical projects include the *in vivo* mapping of cerebral transmitter receptors, evaluating the effects of trophic factor stimulators and lipid peroxidation inhibitors, and pathogenetic and therapeutic studies of motor response complications in parkinsonian patients.

Molecular pharmacological projects within the Branch currently involve studies of D-1 and D-2 dopamine and excitatory amino acid transmitter receptors. Efforts are focused on receptor purification, characterization of receptor-G protein interactions, biochemical mechanisms of receptor regulation, and molecular cloning and characterization of the receptor subtype genes. In addition, the regulation of gene expression in the central nervous system is studied. Both whole-animal and cell culture models are utilized to examine the relation between cell-surface receptors, second messenger systems, and

protein phosphorylation in the regulation of transcription. Ongoing projects include the isolation of transcription factors that regulate the pro-opiomelanocortin gene, characterization of transcriptional mechanisms in models of neurogenic hypertension, and characterization of second messenger systems in the basal ganglia.

- **Physiological Neuropharmacology Section—**
Judith R. Walters, Ph.D.

Studies in the section are directed toward investigation of the effects of drugs on neuronal activity and neurotransmitter function in the CNS, especially in the basal ganglia and associated areas, including the substantia nigra, striatum, and globus pallidus. Extracellular single-unit recording procedures and iontophoretic techniques are employed to explore the mechanisms through which drugs and specific neurotransmitters affect information processing in these brain regions. Currently, the functions of dopamine, GABA, and peptide-containing neurons are being investigated *in vivo* in the rat, with special focus on interactions between processes induced by stimulation of different dopamine receptor subtypes and on modulatory interactions between different neurotransmitter systems. Neurophysiologic determinations are combined with chronic or acute drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

Laboratory of Molecular and Cellular Neurobiology—

- **Section on Membrane Biochemistry—**
Peter H. Fishman, Ph.D.

This section's research involves the biosynthesis, organization, and function of cell-surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. The hormone-stimulated adenylate cyclase and phosphoinositol hydrolysis systems are used as models for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process that leads to stimulation of adenylate cyclase or phospholipase C on the cytoplasmic side of the membrane. Prolonged stimulation results in both desensitization, where the transduction process becomes

attenuated, and in down-regulation, where the receptors become internalized and degraded. The section also is exploring the biosynthesis and function of complex glycosphingolipids known as gangliosides. Gangliosides can function as receptors for bacterial toxins and may be biotransducers of both positive and negative signals that regulate cell growth and differentiation.

Laboratory of Neurochemistry—

Harold Gainer, Ph.D.

This laboratory investigates the cellular and molecular biology of neuropeptides and specific macromolecules involved in the structure and function of the nervous system. Among the peptidergic neuronal systems under study are oxytocin, vasopressin, opioid, LHRH, and CRF-synthesizing hypothalamic cells. Techniques employed include immunochemistry, immunoassay, immunocytochemistry, recombinant DNA methodology, enzymology, protein and peptide separation and chemistry, electrophysiology, and tissue culture. The laboratory uses the approaches of cell biology to study the intracellular and extracellular mechanisms that determine the expression of specific neuronal identity (i.e., the neuron's endogenous peptides, particular projection pathways, and specific termination sites in the central nervous system) and development. In addition to studies of peptidergic neurons, the roles of various proteins (e.g., Na^{2+} - K^{+} -ATPase, protein kinases and phosphatases, neurofilaments and other neuron-specific cytoskeletal proteins, etc.) in neuronal structure and function are studied in both adult and developing nervous systems.

Laboratory of Experimental Neuropathology—

Henry deF. Webster, M.D.

The Cellular Neuropathology Section conducts research on cellular and subcellular mechanisms of myelin formation and maintenance. It develops and uses a broad range of techniques to identify abnormalities in myelin structure, chemistry, and function that lead to myelin breakdown of the type seen in multiple sclerosis, other demyelinating diseases, and experimental myelin lesions. It also investigates cellular mechanisms of myelin regeneration, especially those relevant to the central nervous system.

The Neurotoxicology Section conducts basic research on toxins that induce disease or malfunction of the central and peripheral nervous systems. Among its goals are to elucidate cellular and subcellular mechanisms of neurotoxin actions and to develop correlations between neurotoxicity and dysfunctions in behavior and biochemistry. Researchers in this section investigate toxic mechanisms of neurological disease, conducting collaborative studies with other clinical or basic science components of the National Institute of Neurological Disorders and Stroke as appropriate. Finally, this group utilizes neurotoxins to develop animal models of neurological disorders.

**Alcohol, Drug Abuse,
and Mental Health
Administration**

Frederick K. Goodwin, M.D.

Director

Steven M. Paul, M.D.

Acting Director, Intramural Research

Dennis L. Murphy, M.D.

Associate Director for Clinical Research

Michael J. Brownstein, M.D.

Associate Director for Basic Research

Rex W. Cowdry, M.D.

Deputy Director for Research at Saint Elizabeths Hospital

David R. Rubinow, M.D.

Clinical Director

Darrell G. Kirch, M.D.

Medical Director at Saint Elizabeths Hospital

The National Institute of Mental Health (NIMH) offers an opportunity for post-doctoral training in neuropsychiatric research and in biologic and behavioral sciences. The NIMH intramural program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Most medical staff fellows conduct clinical and/or basic research, and participate in the clinical care of patients admitted as part of clinical research programs. Other fellows engage primarily in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All medical fellows participate in tutorial seminars, other teaching programs, and formal, graduate level courses as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all medical staff fellows to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

**Appointments in Clinical
Research**

The NIMH recruits about 12 new medical staff fellows each year who are primarily involved in clinical research. Appointments normally begin July 1 and are usually for 2- or 3-year periods, although in some instances they may be extended.

Fellows usually begin their appointments after the PGY-3 or PGY-4 level of residency training. Exceptionally well-qualified individuals, however, may be appointed after PGY-2 level of residency training in psychiatry, neurology, or other clinical specialties. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Medical Staff Fellowship Program are now being accepted for July 1991 appointments. Since selections for these positions will be made in January 1990, PGY-2 or PGY-3 psychiatric residents may now apply.

Medical staff fellows usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the fellow and the status of the clinical research program. Intensive clinical supervision on the inpatient psychiatric unit is available from senior psychiatrists. Candidates desiring more information about clinical fellow positions should write to Clinical Director, NIMH, Building 10, Room 3N234, National Institutes of Health, Bethesda, MD 20892.

Appointments in Laboratory Research

Some fellows work primarily in the laboratory under the preceptorship of a senior staff scientist. They are usually matched to a basic science laboratory for comprehensive training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about these positions in the neurobiologic area, contact the chief of the particular basic science laboratory or section at the NIMH.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Clinical and Basic Research Branches

Biological Psychiatry Branch—

Robert M. Post, M.D.

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including depressive, manic-depressive, schizo-affective, panic-anxiety, and menstrually related mood disorders. The focus of the branch is psychobiologic and brings together information from the following disciplines—psychiatry, psychology, neurology, pharmacology, and biochemistry. Longitudinal evaluation of the course of illness and response to treatment is an important clinical and research methodological approach. Specific research interests include behavioral pharmacology, the biochemistry of neurotransmission, neuroendocrinology, investigations of perception and cognition, electrophysiology, epilepsy, and positron emission tomography. A general goal of this branch is to develop programs to investigate psychologic, biochemical, and neuroanatomic contributions to the study of manic-depressive illness, anxiety disorders, and related syndromes.

Fellows will be trained in clinical research methodology, data analysis, and clinical management of research patients. Opportunities are also available for studying behavioral and biochemical laboratory techniques with Drs. Agu Pert, DeMaw Chuang, and Susan Weiss.

- **Section on Psychobiology—**

Robert M. Post, M.D.

A 14-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients with manic-depressive and schizo-affective illness and rapidly cycling affective symptoms. Medical staff fellows are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduct, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic

correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies, such as the measurement of amine metabolites, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely correlated with several biochemical laboratories. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including anti-convulsants such as carbamazepine, valproate, and clonazepam, and several peptides are being explored, especially CRH, TRH, and somatostatin. The mechanisms underlying the paradoxical antidepressant effect of one night's sleep deprivation are studied. Clinical and laboratory studies of cocaine effects on mood and behavior are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis (Dr. S. Weiss). Dr. Agu Pert also conducts major programs on behavioral pharmacology, *in vivo* receptor autoradiography, and the interaction of peptide and neurotransmitter mechanisms. Dr. Marangos studies biochemical mechanisms related to benzodiazepine and adenosine receptors, and calcium channels. Dr. Nakajima is elucidating the regional induction in brain of the c-fos proto-oncogene C-fos using *in situ* hybridization.

- Section on Anxiety and Affective Disorders—
Thomas W. Uhde, M.D.

This unit is engaged in the clinical and laboratory study of patients with anxiety and affective disorders. Most clinical research is conducted in the new Ambulatory Care Research Facility (ACRF), although intensive diagnostic assessment and drug treatment is available to patients on the 14-bed inpatient unit of the Biological Psychiatry Branch. A major emphasis is the study of the phenomenology, life course, neuroendocrinology, biochemistry and physiology of panic disorder, social phobia, generalized anxiety disorder, blood-illness-injury phobia and major affective illnesses associated with panic attacks or obsessive-compulsive symptomatology. Particular attention is given to the development of chemical models of

“awake” and “sleep” panic attacks. This unit also investigates possible “state” or “trait” markers of pathological anxiety and affective states. Testing of new anxiolytic agents is conducted in both inpatient and outpatient programs. Recently investigated drugs have included alprazolam, carbamazepine, clonidine, propranolol, R015-1788, verapamil, nifedipine, and diazepam. Current biologic indices of interest include galvanic skin response, evoked potentials, sleep architecture, pain sensitivity, platelet binding parameters (^3H -dihydroergocryptine, ^3H -imipramine, ^3H -clonidine, ^3H -yohimbine) and the neuroendocrine and biochemical responses to TRH, CRH, GHRF, glucose, clonidine, imipramine, yohimbine and caffeine. These clinical investigations are complemented by basic research in our neurochemistry laboratory and the use of a new animal model of nervous pointer dogs.

- Section on Peptide Studies—

David R. Rubinow, M.D.

This unit is involved in investigating basic mechanisms and clinical manifestations of endocrine and immune effects on mood, cognition, and behavior. CSF, plasma and saliva samples are assayed for peptide and steroid hormone levels. The interface between medicine and psychiatry is explored in a variety of inter-Institute collaborative research projects established through the NIMH consultation-liaison service. An additional major focus is the biological characterization and treatment of menstrual cycle-related mood disorders. These disorders are employed as models for investigation of the biology of the “switch” and selected aspects of behavioral state regulation.

- Unit on Behavioral Pharmacology—

Agu Pert, Ph.D.

This laboratory is concerned with studying the functional activity of specific neural systems in the brain during the various physiological, behavioral, and pharmacological states. Techniques employed include *in vivo* autoradiography, microdialysis and 2-deoxyglucose for assessment of regional cerebral metabolism. Interactions of classical neurotransmitter and peptide substances are elucidated in naturally occurring and in pharmacological models such as behavioral sensitization to psychomotor stimulants. Functional activity of neurochemical and peptide systems are studied during

stress, brain stimulation, reward and other behavioral states pertinent to mood and anxiety disorders.

- **Unit on Receptor Pharmacology—**

De Maw Chuang, Ph.D.

This group conducts research in several areas related to molecular pharmacology. These include studies on: 1) molecular events of internalization of beta-receptors in cells desensitized with beta-receptor agonists; 2) mechanisms of action of antidepressant drugs with special emphasis on the physiological and pharmacological roles of high affinity recognition sites for these drugs; 3) comparative effects of lithium carbonate and carbamazepine; 4) studies of the biochemical mechanisms underlying the long-term changes involved in sensitization and kindling; and, 5) regulation by neurotransmitters and neuromodulators of phospholipid metabolism by phospholipases C and A2 in primary cultures of neurons, cultured tumor cells, rat aorta, and brain slices.

Clinical Psychobiology Branch—

Thomas A. Wehr, M.D.

This branch investigates the pathogenesis of affective illness and develops new methods for its treatment. The results of ongoing work indicate that changes in behavioral factors, such as sleep, and environmental factors, such as light and temperature, can trigger or terminate affective episodes. These factors appear to exert their effects via hypothalamic mechanisms that, at their highest level of integration, control energy homeostasis. The possibility that antidepressant drugs may act via these same mechanisms is also being investigated.

Functions which are regulated by these mechanisms, and which are currently the focus of investigation, include sleep, nutrition, metabolism, motor activity, circadian and seasonal rhythms, and pituitary, thyroid, adrenal and pineal secretions. These variables are often measured longitudinally during procedures, such as sleep deprivation or phototherapy, that rapidly alter clinical state. An effort is made to devise critical experiments to test hypotheses about causes of the illness and mechanisms of these treatments. Sometimes experiments require that patients be treated and monitored in unusual conditions in which environmental time cues, lighting,

temperature, diet, activity, and sleep can be controlled and manipulated.

The clinical investigations are complemented by basic research in animals. In carefully controlled environmental conditions in one of our laboratories motor activity, temperature, metabolic rate, food intake, sleep, and circadian rhythms are continuously monitored in rodents during treatment with antidepressant medications. In another laboratory, effects of light on immune function, which were detected during phototherapy of seasonal depression, are being investigated in animals.

The branch provides an opportunity to acquire the skills and scholarship necessary to conduct clinical research in psychiatry. It also provides an opportunity to participate fully in a vigorous ongoing research program which has pioneered, and which continues to explore, fundamentally new areas in research and treatment of the affective disorders.

Inpatient Research Unit—

Thomas A. Wehr, M.D.

Norman E. Rosenthal, M.D.

The focus of the 15-bed inpatient unit is the intensive investigation of patients with affective disorders and normal controls. Various aspects of behavior and physiology are measured continuously, around the clock, in order to critically evaluate neurotransmitter, neuroendocrine and chronobiological hypotheses of depression. A causal relationship between changes in the sleep-wake cycle and changes in affective state is suggested by the fact that switches from depression into mania occur in close association with dramatic changes in sleep duration, and that a single night of total sleep deprivation can cause patients to switch out of depression, sometimes into mania.

Considerable effort is devoted to experiments designed to elucidate the mechanism of action of sleep deprivation and other sleep therapies of depression. Results indicate that there may be related disturbances in thermoregulation and thyrotropin secretion in depression, reflected in elevated temperature and reduced TSH secretion at night, and that these abnormalities may be partially corrected by sleep deprivation.

Both non-pharmacological and pharmacological treatments, and their interactions, are studied on the inpatient unit. Non-pharmacological treatments include total and partial sleep deprivation, altered sleep schedules, and phototherapy. Pharmacological treatments include hypermetabolic thyroxine therapy and conventional thymoleptic drugs.

Outpatient Research Unit—

Norman E. Rosenthal, M.D.

This unit concentrates on identifying and defining novel groups of patients, and treatments for patients, with affective sleep disorders. Such groups include patients with seasonal affective disorders (either winter or summer depressions) and delayed sleep phase syndrome, people who describe themselves as extreme “night owls.” Treatments we have developed include the use of light and temperature manipulations to modify mood and sleep patterns. The focus of the research shifts between testing hypotheses and generating new ones. Collaboration between groups is encouraged to take advantage of the wealth of expertise available at the NIH.

Our explorations have ventured beyond the areas of obvious interest, like effects of light on pineal function, into studies on the effects of light on information processing (event related potentials) and on the immune system. However, the questions always return to exploration of those behaviors and brain regions that we regard as centrally involved in the illnesses we study.

Many treatment protocols are carried out by patients in their own homes, but there is close co-operation between outpatient and inpatient units so that patients can easily be hospitalized for studies or treatment protocols. An emphasis is placed on developing meaningful questions and testing them with innovative experiments.

Clinical Neuroscience Branch—

Steven M. Paul, M.D.

The branch conducts a multidisciplinary program in basic and clinical neuroscience and attempts to integrate data on the biochemistry and pharmacology of the central nervous system with an understanding of the pathogenesis and treatment of major psychiatric diseases. Structurally the Neuroscience

Branch consists of four sections: Molecular Pharmacology, Preclinical Studies, Brain Biochemistry, and Clinical Studies. Medical staff fellows are assigned to the clinical research unit, usually for a period of 2 or 3 years. During this time their activities are divided between direct patient care, clinical research, and laboratory research, depending on the interests and talents of the individual. Medical staff fellows will be encouraged to become actively involved in ongoing research projects, as well as to develop their own research protocols as early as possible. Collaborations between individual medical staff fellows and the three basic science sections, on both laboratory and clinical research projects, will also be encouraged. The overall goal of the branch is to create a climate in which sound scientific findings can be applied to an understanding of both normal and abnormal behavior.

- Section on Preclinical Studies—

Steven M. Paul, M.D.

The major interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible, basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: 1) biochemical and pharmacologic characterization of the recognition sites; 2) isolation and characterization of the endogenous modulators of these sites; 3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); 4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; 5) behavioral and pharmacologic experiments in animals; 6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes that correlate with the behavioral manifestations of these genetic mutations; and 7) post-receptor events, including alterations in calcium transport and cyclic nucleotide levels.

- Molecular Neurogenetics Unit—
Edward Ginns, M.D., Ph.D.
Brian Martin, Ph.D.

The research in this unit is part of an effort to better understand the molecular mechanisms underlying human nervous system development and function, as well as the pathogenesis of certain neurologic and psychiatric diseases. Our clinical investigation of neurogenetic disorders is closely linked to our basic research programs for the development of techniques for improved diagnosis (RFLP and mutation analysis) and recombinant DNA strategies for therapy. Our studies focus on lysosomal storage disorders, bipolar affective illness, schizophrenia, and related neurogenetic diseases. DNA probes and candidate genes are being isolated from chromosome 11 to study linkage of bipolar affective illness in the Amish and a locus at the end of this chromosome. We are describing the structural and active site properties of lysosomal hydrolases, nervous system proteins (particularly those that interact with pharmacologic agents, excitable membranes and/or receptors), and venom toxins. The cell-specific and developmentally regulated expression of proteins within the nervous system is investigated using the neuron specific (NSE) and non-neuronal (NNE) enolase isozymes as a model. The genomic organization and regulation of expression of human tyrosine hydroxylase, tryptophan hydroxylase and other genes involved in neurotransmitter synthesis that may be related to the pathogenesis of neuropsychiatric disorders are studied. Therapeutic approaches for selected inherited disorders (for example Gaucher disease and Fabry's disease) utilizing retroviral mediated somatic cell gene transfer are being examined using both cell culture models and bone marrow transplantation.

- Section on Brain Biochemistry—
Candace B. Pert, Ph.D.

The section conducts basic neuroscientific and immunological research to understand neuropeptides and their receptors as a communicating network joining the brain, glands, and immune system. Since these components are believed to represent the biochemical substrate of emotion, the theory that psychosomatic aspects of diseases are mediated by this network is of major importance in collaborating experiments with various clinical groups throughout the NIMH/NIH campus.

Laboratory methods include: a) chemical neuroanatomical mapping of neuropeptides and their receptors, which now include growth factors and lymphokines, including endogenous ligands for the T4 (AIDS) virus receptor; b) neuropeptide receptor-mediated chemotaxis of human monocytes provides a readily accessible tissue for assessing neuropeptide function in clinical and normal populations while we attempt to understand the significance of neuropeptide-mediated immune cell trafficking which does occur *in vivo*; and c) the molecular biology of receptors (cell surface antigens) are studied with gel electrophoresis following cross-linking of small peptide ligands onto their recognition molecules, as well as immunoprecipitation and immunoblotting.

The section has a special interest in exploring the hypothesis that schizophrenia is a virally triggered autoimmune disease by molecular analysis of body fluids from schizophrenics and controls. The recent realization that most viruses use cell surface receptors, previously studied as neurotransmitter and drug receptors, to gain entry into cells for subsequent infection has spurred our emphasis on receptor virology. The section emphasizes team work and mutually beneficial cooperating networks of scientists as opposed to hierarchical competitive units as its strategy for efficient and pleasurable work.

- Section on Molecular Pharmacology—

Steven M. Paul, M.D., Acting

Current investigations are directed toward an understanding of the regulation of actions of receptors at the cellular level. Two examples of current work are studies of: interactions between GABA receptors and benzodiazepine receptors; the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity. In addition studies on the mechanisms that control the number and functioning of GABA receptors *in vivo* and *in vitro* and alterations in GABA receptor-coupled chloride ion conductance that occur following exposure of cells to agonists (desensitization) are ongoing. More recent work on the expression of the GABA receptor subunits following chronic drug administration (using specific cDNA probes) are designed to understand the mechanisms of tolerance and dependence. Finally, studies on stress-induced alterations in GABA receptor function have revealed region-specific changes in receptor number. The mechanism(s) (post-

translational modification, changes in transcription, etc.) underlying such change are now being delineated.

- Section on Clinical Studies—

David Pickar, M.D.

This unit encompasses the entire inpatient evaluation and treatment of patients on the clinical research unit. Current research problems include investigations of the clinical phenomenology of schizophrenia and the similarities and differences between schizophrenia and schizo-affective disorders. Studies on the role of central and peripheral opioid systems (i.e., enkephalin, β -endorphin) in stress, schizophrenia, and depression, and in patients with acute and chronic pain are also ongoing. Laboratory investigations on possible peripheral biologic markers in schizophrenia, as well as various affective disorders (i.e., platelet [^{3} H] imipramine binding, serotonin transport, RBC membrane fluidity), are being carried out in hopes of unraveling vulnerability factors in these disorders.

Other areas of interest involve attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of GABA, neuropeptides (such as endorphins and vasopressin), and other neurotransmitter systems for their potential involvement in psychosis; evaluation of new antipsychotic drugs; assessment of pharmacologic and endocrinologic aspects of schizophrenia and schizo-affective illness; immunologic aspects of schizophrenia; study of CAT scan abnormalities; cognitive and psychophysiologic evaluation; and PET scan studies.

Clinical Neuroendocrinology Branch—

Philip W. Gold, M.D.

The Clinical Neuroendocrinology Branch explores the endocrine functions of the brain, the mechanisms of physical and emotional stress and the relevance of stress-responsive neurohormones to the pathophysiology of psychiatric illnesses such as major depression and anorexia nervosa. Melancholic and atypical depression is studied. The interactions between the CRH and locus ceruleus-norepinephrine systems are studied utilizing paradigms such as the continuous monitoring of lumbar CSF for 30 hours and the assessment of basal and

stimulated norepinephrine spillover into arterial blood. Anorexia nervosa and bulimia also are studied. Neural mechanisms subserving hunger and satiety which may confer pathophysiological specificity upon the eating disorders as well as possibly influencing their marked female preponderance are studied.

Neurobiological parameters in patients with major endocrine disorders such as Cushing's disease are researched. Recent work has elucidated pathophysiological differences between major depression and Cushing's disease and has led to methods of determining differential diagnosis. Postdoctoral fellows all work closely with the principal endocrine group at the NIH Clinical Center and obtain in-depth training in endocrinology and neuroendocrinology. Fellows have the opportunity to take a pre-clinical research course. Techniques such as *in vitro* mutagenesis and *in situ* hybridization are used in the molecular biology laboratory. Other laboratory studies employ high resolution autoradiography, immunocytochemistry and the techniques of behavioral pharmacology.

- Unit on Functional Neuroanatomy—
Miles Herkenham, Ph.D.

Anatomical methods such as immunohistochemistry, *in situ* hybridization histochemistry, and receptor autoradiography are used to show sites of transmitter synthesis, release, and binding. Studies of the anatomical basis for the stress response are in progress, using primates as well as rats in animal models of depression. The consequences of acute and chronic stress are measured using mRNA probes for tyrosine hydroxylase and hypothalamic peptides. We are also localizing receptors for opioid peptides, dopamine, and cannabinoids, and sites of action of neurotoxins. This unit combines molecular and neuroanatomical methods to reveal forms of intercellular and intracellular communication in the brain. Changes in levels or distributions of "informational substances" and their associated receptors are achieved through surgical or drug manipulations, and these are assessed by quantitative techniques, including quantitative autoradiography, radioimmunoassay, and HPLC.

Laboratory of Clinical Science—

Dennis L. Murphy, M.D., Acting

This laboratory conducts research on the biochemistry and pharmacology of the nervous system and relates these findings to clinical areas in psychiatry, medicine, and neurology. The laboratory consists of five sections, one with a predominantly clinical orientation and four emphasizing basic research on brain function and behavior.

- **Section on Clinical Neuropharmacology—**

Dennis L. Murphy, M.D.

This section conducts clinical and laboratory studies designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with obsessive-compulsive affective disorders, dementias (e.g. Alzheimer's disease), obsessive-compulsive symptoms, and other behavioral disorders. The clinical studies are primarily based on a 10-bed psychiatric research ward. The inpatient investigations are complemented by an outpatient program for the longer-term study of obsessive-compulsive and dementia patients.

Support for the clinical studies includes a biochemistry/neuroendocrine laboratory and a behavioral assessment and data processing program. Other neurochemical laboratory studies are oriented toward monoamine neurotransmitter receptor function and brain peptide interactions with monoamine systems. Facilities for nonhuman primate studies and behavioral studies of drug effects in small animals are also available in the section.

The ward research investigations, which are balanced between biologicpharmacologic and psychologic-phenomenologic approaches, take place in the setting of an active clinical treatment program. The incoming medical staff fellow, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the fellow will work with a senior staff member in the planning, design, and implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research and laboratory approaches to clinical problems. Specific research projects range from psychobiological studies

of the characteristics of individuals who do or do not respond to specific drugs and to laboratory or animal studies of the effects of drugs on neurotransmitter receptor functions and other cellular events. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include serotonergic agonists and antagonists, selective monoamine oxidase inhibitors, and cholinergic agents including scopolamine, nicotine, and other cholinergic agonists, and some new investigational compounds. Special areas of study at present include investigations of adaptational responses to long-term drug administration in neurotransmitter receptors and secondary effector systems; animal models of affective and cognitive disorders; neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; and methods for the assessment of behavioral and psychological states.

- Section on Histopharmacology—

David M. Jacobowitz, Ph.D.

This section studies unusual proteins in the brain and other areas of the body that will generate antisera which can be used as immunological probes in order to reveal neuronal circuitry, cell classes and other interesting structures in the brain and periphery. Two-dimensional gel electrophoresis and column chromatography are being used for the isolation and purification of brain proteins. Immunocytochemical methods are used to study the brain. Cell cultures are used to study proteins within astrocytes. Proteins in brain tissue of human pathologies such as schizophrenia, Alzheimer's disease, tumors, etc. are being studied. Molecular biological techniques are available for protein sequencing and gene exploration.

- Section on Analytical Biochemistry—

Sanford P. Markey, Ph.D.

The major interests of this section are the development and application of new technologies to study human metabolism and pharmacology. Currently, major areas of interest are amplified enzymelinked immunoassay as applied to MPTP-induced parkinsonism; the pharmacokinetic analysis of stable isotope-labeled neurotransmitters in man; and the development of new mass spectrometric methods of biochemical analysis.

Areas of study include: 1) the mechanism of action of the neurotoxin MPTP, and the relevance of this neurotoxin to idiopathic Parkinson's disease. Antibodies to MPTP and its principal metabolite MPP⁺ will be used in ELISA and immunocytochemical assays to query whether there are MPTP-like neurotoxins in the environment, as well as the subcellular distribution of MPTP metabolites in brain; 2) understanding normal neurotransmitter turnover in man using carbon-13 labeled norepinephrine; and 3) develop techniques suitable to the analysis of difficult to analyze compounds, especially neuropeptides, using laser desorption-Fourier transform mass spectrometry. New instrumentation permits sensitive and selective detection which will be employed to detect and quantify compounds with molecular weights below 5000.

- Section on Clinical Pharmacology—

William Z. Potter, M.D., Ph.D.

The central focus is the study of the mechanisms of action of antidepressants and other psychoactive drugs as a means of exploring the etiology of psychiatric illnesses. Current clinical studies include patients with severe unipolar or bipolar illness as well as normal volunteers. Both putatively specific drugs and ECT are examined to identify common biochemical effects using neurotransmitter measures in cerebrospinal fluid, plasma and urine in humans. Parallel investigations are done in animals. Models for examining the interactions of systems or the effects of treatments on such interactions are emphasized so as to test hypotheses of dysregulation of systems in neuropsychiatric illnesses.

- Clinical Research Unit—

Matthew Rudorfer, M.D.

The unit operates as part of a 15-bed psychiatric research ward which focuses on patients with affective illness. Subjects are intensively investigated following a minimum 3-week drug-free period using baseline measures of catecholamines including lymphocyte receptors and neuroendocrine responses to serotonin uptake inhibitors. Peptidergic measures of CSF are obtained through ongoing active collaborations. The mechanism of action of ECT is of particular interest. Animal models for the human studies are developed under the direct supervision of the Section Chief.

- Unit on Clinical Neurochemistry—
Ivan Mefford, Ph.D.

The unit runs a state-of-the-art HPLC laboratory which measures monoamine clinical research samples within the Intramural Program. A GC-MS component is routinely available for assay validation. The unit performs basic research on understanding the role of neurotransmitters. Currently, the focus is on whether epinephrine is a neurotransmitter in the central nervous system.

- Unit of Preclinical Neuropharmacology—
Juan Saavedra, M.D.

The unit is involved in research on the function of brain neuropeptides and biogenic amines. The main focus is on the central regulation of pituitary function and autonomic (mainly cardiovascular) activity. The unit is also interested in the interactions between the nervous, endocrine and immune systems. There is active research on the localization and regulation of receptors for hallucinogens and on the function and regulation of the brain dopamine system. The current research combines neuroanatomical, autoradiographic, biochemical and molecular biology techniques to study the metabolism of neuromodulators in discrete brain nuclei and peripheral organs. In addition the unit is actively involved in the development of quantitative autoradiographic methods to characterize neuropeptide and biogenic amine receptors in human blood cells, and in the application of these methods to clinical studies.

- Section on Biomedical Psychiatry Therapeutics—
Dennis L. Murphy, M.D.

This section studies the psychobiology of the eating disorders anorexia nervosa and bulimia nervosa with comparisons to affective and anxiety disorders. Patients are studied as inpatients on a behaviorally-oriented clinical research unit to allow longitudinal assessment of physiological and psychological measures during nutritional stabilization and weight restoration. Current studies include neuroendocrine and behavioral responses to pharmacological challenges to test hypotheses implicating altered serotonin, norepinephrine and opiate function in the eating disorders. Other areas of study include amine metabolites and neuropeptides in cerebrospinal fluid of patient and controls, and state related changes in energy metabolism

(assessed by indirect calorimetry). Therapeutic trials with a serotonin agonist and an opiate antagonist are being conducted in the outpatient clinic.

Preclinical studies in the section complement the clinical investigations, with a current focus on opiate and monoamine mechanisms involved in appetitive responses in laboratory animals. Analytic methodologies in use in the laboratory for clinical and preclinical studies include HPLC, GC-MS, and radioimmunoassay.

Child Psychiatry Branch—

Judith L. Rapoport, M.D.

This branch studies biological correlates of childhood behavioral and developmental disorders. There is a six bed day and/or overnight hospitalization inpatient program and other beds as needed on a pediatric ward, as well as an active outpatient program.

The focus of the program is on diagnostic biological measurements appropriate for childhood disorders and on the identification of biological risk factors for impulse and developmental disorders.

The program includes studies of the diagnostic assessment and drug treatment of hyperactive/conduct disordered children, pharmacokinetic studies, and studies of neurotransmitter systems via body fluids.

A unit is conducting brain imaging studies, in children with developmental disabilities utilizing a variety of techniques. Another group is studying the diagnosis, treatment response and followup status of children and adolescents with severe primary obsessive compulsive disorder.

Clinical Neurogenetics Branch—

Elliot S. Gershon, M.D.

The Clinical Neurogenetics Branch conducts studies of the molecular and biochemical genetics of neuropsychiatric diseases. Applications for Fellowships are considered from those individuals with an expressed interest in understanding the genetics of these illnesses. Basic science studies relevant to the understanding of molecular and biochemical genetics are also conducted.

- Section on Clinical Genetics—

Elliot S. Gershon, M.D.

Several types of clinical investigations are conducted, including family studies on the inheritance of neuropsychiatric diseases, molecular genetic research on possible causative genes, peripheral receptor studies, pharmacologic challenges and studies on cerebrospinal fluid. These projects are conducted in an attempt to define biological and/or molecular genetic trait markers in neuropsychiatric diseases.

Currently, an emphasis is placed on using molecular genetic techniques to evaluate the role of CNS-related genes (particularly neurotransmitter receptor genes and neuropeptide genes) in the inheritance of genetic diseases of the brain.

Additionally, new mathematical genetic approaches to the understanding of inherited behavioral phenomena are employed, including multi-point linkage mapping and computer assisted modeling of inheritance patterns in relevant diseases.

- Section on Biochemical Genetics—

Carl R. Merrill, M.D.

This section conducts research on genomic and gene product variations and studies their relations to inherited disorders. Ongoing research includes the identification of abnormal proteins in cerebrospinal fluid. Disease specific cerebrospinal fluid proteins have been found in Creutzfeldt-Jakob disease, herpes encephalitis, schizophrenia, multiple sclerosis and Parkinson's disease. Efforts are currently under way to determine the primary structure of these proteins so that gene probes can be synthesized to determine whether they are of human origin.

Polymorphic proteins are being used to search for linkage with genetic diseases involving the central nervous system. Both of these protein studies utilize high resolution two-dimensional gel electrophoresis. The section has developed ultra sensitive silver strains for the detection of proteins and nucleic acids. Methods to further increase the sensitivity and specificity of protein detection are under development.

The section is also studying the mitochondrial genome in the central nervous system as a means of determining the somatic mutation rate in this organelle in an aging postmitotic tissue, and in individuals with diseases displaying nonmendelian ma-

ternal inheritance patterns. Hybridization and DNA sequencing techniques are being utilized.

Laboratory of Cell Biology—

Michael J. Brownstein, M.D., Ph.D.

The members of this group have a variety of research interests. These include light and electron microscope-level neuroanatomy, chronobiology, developmental neurobiology, biosynthesis of biologically active molecules, isolation of novel peptide hormones, and regulation of intracellular processes by chemical messengers.

Laboratory of Developmental Psychology—

Marian Radke-Yarrow, Ph.D.

A broad program of research is conducted on the behavioral child development, including cognitive, social and emotional functioning. Of special emphasis are studies of children at risk for psychological and psychiatric problems. Children of depressed parents, children who have suffered sexual abuse and young children who manifest extremely aggressive behavior are studied. Longitudinal investigational approaches are used. Comparison groups of children from pathological backgrounds are included. Psychological, environmental and biological mechanisms are investigated from a developmental perspective. Other studies focus on normal adolescents and the interrelations of biological (endocrine and physical growth) factors and psychological and behavioral factors.

Developmental psychologists and child psychiatrists are on the staff. Many of these studies involve research collaborations with colleagues in other laboratories and universities throughout the country.

Laboratory of Psychology and Psychopathology—

Allan F. Mirsky, Ph.D.

This laboratory conducts a broad program of basic and clinical research on normal and impaired attention, learning and memory in humans and on the neurophysiologic and psychophysiological mechanisms involved in these processes. There is a strong emphasis, as well, on genetic studies in schizophrenia under the direction of Seymour S. Kety, M.D. and Loring Ingraham, Ph.D. Studies of attention and

autonomic nervous system functioning in schizophrenics and in other patients, and of drug effects on these processes are being done by Theodore P. Zahn, Ph.D.

Investigations of attention and cortical and brainstem event-related potentials and eye-blink reflexes in psychiatric and neurologic patients are under way. This work takes place in the laboratories of Connie C. Duncan, Ph.D. and Bruno J. Anthony, Ph.D. These assays are used to evaluate information processing deficits in these patients. Also studied are children with attention deficit disorder, Tourette's syndrome and related conditions. The laboratory also participates in large-scale epidemiological studies of attention-related behavior in the Baltimore Public Schools, and in selected high-risk populations in the U.S.A., Israel and Ireland.

Laboratory of General and Comparative Biochemistry— Giulio L. Cantoni, M.D.

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section on Alkaloid Biosynthesis—
S. Harvey Mudd, M.D.

This section studies enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism— Louis Sokoloff, M.D.

- Section on Developmental Neurochemistry—
Louis Sokoloff, M.D.

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of

particular interest are chemical compounds such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of local glucose consumption within the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pharmacological states. The method has been adapted for use in man with PET scanning. Because of the close relationship between local glucose utilization and local functional activity in the nervous system, the method has made it possible to map the entire central nervous system for alterations in local functional activity in various normal and abnormal states. The method is being applied in this laboratory to a variety of neuroanatomical, neurophysiological, neuropharmacological, and neuro-behavioral questions.

Laboratory of Neurochemistry—

Seymour Kaufman, Ph.D.

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy, including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology—

Steven P. Wise, Ph.D., Acting

This laboratory combines the techniques of electrophysiology, neuroanatomy, and behavioral biology in studies aimed at

understanding the brain circuits and cells types in the frontal cortex.

Work in this laboratory combines techniques of basic neurobiology with techniques of single cell recording in operantly conditioned monkeys. The aim of the work is to discover how the different topographic divisions of the frontal cortex interact in behaving organisms. Special attention is devoted to the different sorts of sensory information that are processed in different subdivisions of the somatic sensorimotor cortex and to how behavioral set and intention for future action are reflected in regions such as the premotor and supplementary motor areas of the cerebral cortex.

Neuropsychiatry Branch—

Richard J. Wyatt, M.D., Chief

This branch conducts basic and clinical research in neuropsychiatric disorders, with special emphasis on the dementias and psychoses, especially schizophrenia. The four sections of the branch consist of working groups of investigators employing molecular, biochemical, pharmacological, physiological, and other techniques to examine brain structure and function in an effort to determine the underlying causes of these neurobehavioral disorders.

The Neuropsychiatry Branch is located in the Neurosciences Branch, a facility maintained by the NIMH on the grounds of Saint Elizabeths Hospital in Washington, D.C.; and the majority of clinical studies involve inpatients occupying the 42 beds of the unique research hospital program. The research wards are supervised by NIMH Medical Staff Fellows, with full support by nurses, social workers, ancillary therapists, and technicians. In addition, clinical investigations may involve patients from the campus in Bethesda, Maryland, Saint Elizabeths Hospital, or other facilities.

- **Molecular Neuropsychiatry Section—**

Darrell Kirch, M.D.

Richard J. Wyatt, M.D., Chief

Farouk Karoum, Ph.D.

Henrietta Kulaga, Ph.D.

Ana Hitri, Ph.D.

The main emphasis in this group is on the use of advanced basic science techniques in biochemistry, molecular biology

and genetics, immunology, and virology. The goal is to conduct basic neuroscientific investigations; to search for biochemical, cellular, and genetic abnormalities in neurobehavioral disorders; and to assess the effects of drugs at the cellular and molecular level. High performance liquid and gas chromatography/mass spectroscopy laboratories have been established to measure biogenic amines and psychoactive drugs. RNA isolation and gene cloning techniques are being developed to study disorders at the genomic level. The possible role of autoimmunity and/or viral infection in neuropsychiatric disorders is being examined using molecular and tissue culture techniques. In addition, the pathophysiology of the human immunodeficiency virus is being investigated in relation to the central nervous system effects of AIDS.

- Section on Aging—
Richard J. Wyatt, M.D., Chief
Janice R. Stevens, M.D.
Gad Gilad, Ph.D.

This group conducts basic and clinical research related to a variety of behavioral and degenerative central nervous system disorders, including dementia, movement disorders such as tardive dyskinesia, and epilepsy. A primary emphasis has been on neurotrophic factors and other substances (including pharmacological agents) affecting neuronal differentiation and function, with efforts to develop both *in vivo* and *in vitro* systems to study these factors.

- Section on Preclinical Neuroscience—
William J. Freed, Ph.D., Chief
Gregory Straw, M.D.
Maciej Poltorak, M.D.

This section conducts neuropharmacology and behavioral pharmacology studies in animal models to elucidate the mechanisms of action and interactions among neuroleptics, stimulants, excitatory amino acids, anticonvulsants, calcium channel inhibitors, peptides, and other compounds. Techniques used include studies of behavioral activity, stereotypic and rotational behavior, conditioning, measurements of seizures, receptor binding, and immunocytochemistry of cell adhesion molecules, neurofilaments, and lymphocyte markers.

A second area of research emphasizes the exploitation of brain grafting techniques to correct lesion-induced behavioral

deficits. Currently under study are the characteristics of the brain as a site for transplantation and the potential of brain grafts to effect functional reconstitution. A major success has been in grafting adrenal medulla or substantia nigra to the corpus striatum, thereby correcting the rotational behavior that develops following unilateral substantia nigra lesions. Destruction of the substantia nigra has been considered by many to be an animal model of Parkinson's disease. This section is applying these techniques to rats and monkeys to develop brain grafting within this model. Other interests involve the use of transplantation techniques to study brain development, neuronal plasticity, immunology, and immunocytochemical studies of transplanted brain tissue.

- Section on Clinical Neuropsychiatry—

Richard J. Wyatt, M.D., Chief

David Glovinsky, M.D.

Richard L. Suddath, M.D.

Michael Egan, M.D.

Robert C. Alexander, M.D.

Viola Khoule, M.D.

This section emphasizes research on the biological and behavioral correlates of schizophrenia and related disorders. It conducts clinical pharmacological trials, with a special emphasis on identifying anti-psychotic properties of non-neuroleptic drugs and on exploring new clinical strategies for the prevention and treatment of tardive dyskinesia. In addition, patients are studied using brain imaging, electrophysiology, neuropsychology, and various behavioral rating scales. Samples of blood, urine, and cerebrospinal fluid from patients and normal control subjects are carefully collected for study by basic scientists (in the branch and elsewhere) interested in applying newly developed biochemical, molecular, and immunologic techniques. Data from these diverse basic and clinical approaches are integrated in an attempt to better define the pathophysiology and clinical subgroups of schizophrenia and related disorders.

Clinical Brain Disorders Branch—

Daniel R. Weinberger, M.D.

Joel E. Kleinman, M.D.

The clinical branch is concerned with research on the brain in a number of neuropsychiatric disorders including schizophrenia, movement disorders, and dementia. Approaches to these disorders include neuroimaging, postmortem studies, clinical pharmacological studies, and animals models.

Although some of these studies are conducted at the main campus in Bethesda, Maryland, the majority are done at the NIMH Neuroscience Center-William A. White Research Hospital located on the grounds of Saint Elizabeths Hospital in Washington, D.C. The NIMH Neuroscience Center-William A. White Research Hospital has three 14 bed research wards for patients with schizophrenia and neuropsychiatric disorders.

This group also directs the behavioral neurology service at St. Elizabeths Hospital.

- Section on Neuropathology—

Joel E. Kleinman, M.D., Ph.D.

This section involves postmortem studies of schizophrenia, suicide, alcoholism, other drug addictions, movement disorders, and dementias. A large human brain bank maintained within this section make these studies possible. Varied techniques are employed which include neurochemistry, autoradiography, immunocytochemistry, and neuronal morphometrics. In addition, animal models of neuropsychiatric disorders are investigated with these techniques. Non-human primate studies are an integral part of the work of this section. A team of psychiatrists, neurologists, and neuropathologists collaborate on these projects.

- Section on Clinical Studies—

Daniel R. Weinberger, M.D.

This section involves studies on patients with neuropsychiatric disorders, especially schizophrenia and dementia. The approach is primarily two-fold. One major focus, neuroimaging, involves studies of computer tomography, magnetic resonance imaging, computerized electroencephalography, regional cerebral blood flow and single photon emission computed tomography. A second focus, clinical pharmacological studies, is used to test hypotheses in conjunction with

neuroimaging. A team of psychiatrists, neurologists, neuropsychologists and neuroimaging specialists work together on these projects.

Laboratory of Preclinical Pharmacology—

- Section on Neuropeptides—
Hsiu-Ying T. Yang, Ph.D.

Studies of neuropeptides operative in the regulation of pain threshold are carried out with target on the molecular mechanisms of tolerance and dependence to morphine. Work on this study has contributed to the isolation of a novel peptide with morphine modulating activity. Current studies are on functions of this peptide in CNS with emphasis on the role of this peptide in the development of tolerance. Adrenal chromaffin cell is now known to contain various peptides in addition to catecholamines. This section is also involved in studying the role of peptides in the adrenal function. Current focus is on the role of neuropeptide Y in catecholamine secretion using chromaffin cell culture.

Murray Goldstein, D.O., M.P.H.

Director

Irwin J. Kopin, M.D.

Director, Division of Intramural Research

Ernst Freese, Ph.D.

Director, Basic Neurosciences Program

Mark Hallett, M.D.

Director, Clinical Neurosciences Program

The National Institute of Neurological Disorders and Stroke (NINDS) provides broad opportunities for post-doctoral training in the basic and clinical neurosciences. Laboratories and clinics operated by the Institute are located principally on the main NIH campus in Bethesda, Maryland. Limited training opportunities also exist at the (NINDS) facility in Frederick, Maryland. Most medical staff fellows participate in clinical neurosciences research in Institute laboratories and clinics, and have responsibility for the care of patients admitted for study. Some fellows primarily engage in basic laboratory investigations. All work is conducted under the preceptorship of a senior staff member and fellows are encouraged to avail themselves of an active program of teaching seminars, invited lectureships, and ward rounds.

Appointments in Clinical Research

Medical staff fellow positions for the National Institute of Neurological Disorders and Stroke (NINDS) are available in medical and surgical neurology, epilepsy, motor control, clinical neurophysiology, neuropharmacology, experimental therapeutics, infectious diseases, neuroimmunology, neuroepidemiology, and developmental and metabolic neurology. Fellows are usually appointed for two years, with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on (NINDS) wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current (NINDS) research emphases.

Candidates requiring further information about (NINDS) clinical positions for medical staff fellows should write to Mark Hallett, M.D., Clinical Director, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, Bldg. 10, Room 5N226, National Institutes of Health, Bethesda, Maryland 20892.

Appointments in Laboratory Research

Medical staff fellow positions are available in neurochemistry, neurophysiology, neuropathology, neuro-otolaryngology, biophysics, molecular biology, biology, molecular genetics, and other areas of fundamental neurosciences investigation. Appointments are for two years, with the possibility of extended affiliation.

Areas of study are developed by each fellow in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned. Independence and originality of approach are encouraged.

Medical staff fellows have the opportunity to work closely with a large and diverse group of senior investigators, to participate in on-site courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the (NINDS) Medical Staff Fellowship Program, write to Ernst Freese, Ph.D., Director, Basic Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, Bldg. 36, Room 5A05, National Institutes of Health, Bethesda, Maryland 20892.

Medical Staff Fellows in Pharmacology (PRAT).

Some of the programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in basic or clinical pharmacology. For more information about the PRAT program, see page 177.

Clinical Neuroscience Branch—

Irwin J. Kopin, M.D., Chief

- **Section on Aminergic Mechanisms—**

Irwin J. Kopin, M.D.

The research in this section is focused on fundamental studies of the mechanisms of biosynthesis, storage, release, receptor activation, disposition and metabolism of amine neurotransmitters in the brain and in the peripheral autonomic nerve system. The regulations of these processes during growth, development and regeneration and the effects of stress, drugs, toxins are examined using biochemical, autoradiographic, and immunohistochemical methods. Medical staff fellows are appointed for two or more years and have the opportunity of participating in collaborative research projects as well as developing independent studies in appropriate areas.

- **Section on Clinical Neuropharmacology—**

Ronald J. Polinsky

The section investigates neurotransmitter function and metabolism in various neurological disorders. Assessment of the noradrenergic system in patients with chronic autonomic failure is performed by measuring the levels of catecholamines and their metabolites in blood, urine, and cerebrospinal fluid. Interrelationships among neurotransmitter, hormonal, and peptide systems are examined using several neuroendocrine and neuropharmacological approaches. There is also an experimental treatment program for patients with orthostatic hypotension.

A longitudinal study of clinical, biochemical, and neuropharmacological changes in familial Alzheimer disease is in progress. Collaborative investigations of genetic linkage and analysis in familial Alzheimer disease is being conducted. Other disorders currently studied in this section include narcolepsy, dystonia musculorum deformans, Gilles de la Tourette syndrome, and Parkinson's disease. Initial appointment of medical staff fellows is for two years. Preference is given to candidates with training in clinical neurology.

Development and Metabolic Neurology Branch—

Roscoe O. Brady, M.D.

- **Section on Enzymology and Genetics—**

Roscoe O. Brady, M.D.

Research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic abnormalities in disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with enzyme replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and investigations of genetic mutations of cholesterol metabolism in experimental animals and in humans.

- **Section on Neurochemical Methodology—**

Andrew E. Gal, Ph.D.

This section is involved in the preparation of substrates for the diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, identification of new lipid storage disorders, and the synthesis of lipids and lipid analogs for metabolic studies in normal and pathologic tissues.

- **Section on Molecular and Medical Genetics—**

Stefan Karlsson, M.D., Ph.D., Acting

This section conducts research on the biochemistry and molecular genetics of inherited disorders of metabolism. Work is focused on studies of lysosomal storage disorders and hemoglobinopathies. Projects include cDNA and genomic cloning, gene transfer, expression of genes in bacterial and mammalian cell genetic recombinants, gene assignment, DNA restriction fragment polymorphism, molecular diagnostic methods, production of transgenic animals, and development of gene therapy technology.

- **Section on Clinical Investigations and Therapeutics—**

Roscoe O. Brady, M.D.

Norman W. Barton, M.D., Ph.D.

This section focuses on clinical studies of metabolic disorders of the nervous system with particular attention to lysosomal storage diseases. Trials of novel therapeutic strategies are carried out including enzyme replacement. Gene

replacement or therapy is under consideration. Therapeutic trials are also conducted for hereditary familial ataxias and various other neurologic diseases. Patients with neurogenetic diseases are admitted for diagnosis and evaluation of therapeutic strategies.

Experimental Therapeutics Branch—

Thomas N. Chase, M.D.

- **Pharmacology Section—**

Thomas N. Chase, M.D.

This section conducts an integrated program of preclinical and clinical studies directed towards the rational development of improved therapies for extrapyramidal and dementing disorders. Current investigations focus on the pharmacology of central transmitter systems; biochemical and cerebral imaging (positron emission tomography) approaches are used to related neurologic symptoms to dysfunction of specific classical or peptidergic systems. Pathogenic hypothesis and pharmaceutical mechanisms are explored.

- **Unit on Molecular Pharmacology—**

David R. Sibley, M.D.

This unit investigates the biochemical and molecular characteristics of neurotransmitter receptor-mediated signal transduction. Research is focused on receptor purification and biochemical characterization, elucidation of receptor-effector coupling mechanisms, G proteins, cell biology and biochemical mechanisms of receptor regulation, and molecular cloning and characterization of receptor subtype genes in both normal and pathophysiological states. Primary receptor systems under investigation are for dopamine and excitatory amino acids.

- **Physiological Neuropharmacology Section—**

Judith R. Walters, Ph.D.

Studies are directed toward investigation of the effects of drugs on neuronal activity and neurotransmitter function in the CNS, especially in the basal ganglia and associated areas, including the substantia nigra, striatum, and globus pallidus. Extracellular single-unit recording procedures and iontophoretic techniques are employed to explore the mechanisms through which drugs and specific neurotransmitters affect information processing in these brain regions. Currently, the

functions of dopamine, GABA, and peptide-containing neurons are being investigated *in vivo* in the rat, with special focus on interactions between processes induced by stimulation of different dopamine receptor subtypes and on modulatory interactions between different neurotransmitter systems. Neurophysiologic determinations are combined with chronic or acute drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

- Unit on Neuroendocrinology—

Donald R. Gehlert, Ph.D.

The unit conducts preclinical investigations of regulatory processes in neuropeptide containing neurons. Research will lead toward a better understanding of neurological disease and the development of new pharmacological therapeutic agents. The particular focus is on the mechanisms of regulation of gene expression of neuropeptide prohormones and neuropeptide processing enzymes. The methodologies used in the lab include peptide and protein isolation and structural determinations, western analysis and 2-D electrophoresis, gene cloning and isolation and RNA hybridization assays, neuropeptide receptor identification, and histochemical techniques including immunohistochemistry and *in situ* hybridization.

Medical Neurology Branch—

Mark Hallett, M.D.

- Section on Clinical Epilepsy—

William Theodore, M.D.

The section conducts intensive monitoring of patients with uncontrolled seizures by videotape recording and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents including experimental drugs, studies on the effectiveness of surgery, and studies on the usefulness of new scanning procedures, such as positron emission tomography. Various clinical and electroencephalographic and magnetoencephalographic (MEG) aspects of seizure disorders are investigated, with emphasis on diagnosis and localization. Cerebral evoked response techniques are also applied for clinical and research studies. Basic investigations are focused on pathophysiologic and pharmacologic aspects,

utilizing a kindling model of epilepsy. The appointment of medical staff fellows is for two years.

- **Section on Human Motor Control—**
Mark Hallett, M.D.

This section is concerned with the control of movement in man. Mechanisms of generation of normal movement, pathophysiology of disordered voluntary movement and pathophysiology of involuntary movements are the major interests. Investigations involve careful clinical evaluation, physiological investigation and radiological studies including positron emission tomography. Physiological investigations include electromyography, electroencephalography, and quantitative measures of mechanical movements of the relevant body parts. One unit is primarily interested in limb movement and another unit is primarily interested in balance.

- **Unit on Neuromuscular Diseases and Neuro-AIDS—**
Marinos Dalakas, M.D.

The unit investigates the immunological and virological aspects of neuromuscular disorders such as polymyositis, inclusion body myositis, post polio syndrome and demyelinating polyneuropathies. Research is performed on muscle enzyme histochemistry, and immunocytochemistry of muscle and nerve looking for alterations in the antigenic properties of muscle and Schwann cells.

Another part of this unit investigates the clinical, virological and immunological manifestations of Neuro-AIDS. Patients with a CNS or PNS disease as the first manifestation of HIV infection are investigated with a series of electrophysiological, immunological, virological, histological and radiological studies including PET scans. Therapeutic drug trials are conducted and the efficacy of new antiretroviral agents in HIV-related CNS or PNS diseases is assessed. Fellows perform clinical studies, electrophysiology, muscle/nerve biopsies, enzyme histochemistry and basic research in neurovirology or neuroimmunology.

Neuroepidemiology Branch—

Jonas Ellenberg, Ph.D., Acting

This branch conducts national and international studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The medical staff fellow receives

training in the utilization of neuroepidemiologic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the branch's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurofibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, epilepsy, racial differentials in the occurrence of neurologic disease, and international variation in the occurrence of neurologic diseases.

Neuroimmunology Branch—

Dale E. McFarlin, M.D.

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles and HTLV-1 which cause chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune disease such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of unknown etiology, such as multiple sclerosis and Parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

Surgical Neurology Branch—

Edward H. Oldfield, M.D.

This branch investigates the following: Primary central nervous system tumors of the brain and spinal cord, pituitary tumors, spinal vascular malformations, certain forms of cerebrovascular disease, CNS implantation, and seizure disorders refractory to medical therapy. Clinical research in these areas is combined with laboratory research in cell biology, tissue culture, biochemistry, immunology, pharmacology, endocrinology and light and electron microscopic histology to provide advancements in the understanding of these disorders.

• Section on Clinical Neurosurgery—
Edward H. Oldfield, M.D.

This section performs clinical research with emphasis on patients with primary tumors of the brain and spinal cord, pituitary tumors, vascular disorders of the central nervous system, and epilepsy. Investigation is designed to put findings from the basic laboratories into practice in the clinic. Current projects include 1) investigational treatment of malignant brain tumors with interstitial radioactive implants, intracarotid chemotherapy, phase I and II studies of new chemotherapeutic agents, and immunotherapy; 2) investigation and treatment of arteriovenous malformations of the spinal cord and brain; 3) *in vivo* and *in vitro* investigation of ACTH-, TSH-, and growth hormone-secreting pituitary tumors; 4) the use of positron emission tomography in the investigation of drug delivery, blood-brain-barrier permeability, and the metabolism of brain tumors, and 5) the clinical and laboratory investigation of CNS implantation for Parkinson's disease.

The medical staff fellow participates in the care of patients on the various protocols of the Clinical Neurosurgery Section as well as consultative care of patients with neurosurgical problems in all NIH institutes. There will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, neuroendocrinology, and quantitative autoradiography. Experimental surgery and other studies in animal models as they relate to the clinical problems under study will also be performed. The fellow works in collaboration with senior scientists in specific laboratory areas as his or her experience and interest dictates.

Office of the Clinical Director—
Mark Hallett, M.D.

This office has the responsibility for clinical neurological services to investigators within NINDS and the other Institutes. Activities include clinical neurophysiological laboratory investigations, neurology consultations and neuropathology. Training opportunities emphasize development of clinical skills, but include application of these skills to clinically relevant research.

- EEG Laboratory—

Susumu Sato, M.D.

The EEG laboratory offers both routine electroencephalography and evoked potential studies. Fellowship training satisfies requirements for taking the ABCN examination.

- Electromyography Laboratory—

Roger Gilliatt, M.D.

The EMG laboratory offers routine electromyography and a number of special studies including single fiber electromyography and autonomic nervous system testing. The experience in fellowship satisfies requirements for taking the ABEM examination.

- Clinical Neurology and Neuropathology—

Mark Hallett, M.D.

This division offers neurological consultation services including neuropathology. Research areas include neurological aspects of medical diseases.

- Section on Neuroimaging—

Giovanni Di Chiro, M.D., Chief

This section focuses on emission computed tomography (ECT) using positron emitting radionuclides (positron emission tomography-PET). The section is also actively involved in nuclear magnetic resonance (NMR) and spectroscopy of the central nervous system. Emphasis is placed on correlative studies between PET and NMR, as well as comparison with the more conventional neuroradiological techniques (CT, angiography).

Traditionally, this section has been on the forefront of advanced radiographic and nuclear medicine equipment development. This has been expanded to include NMR imaging-spectroscopy devices (modifications of a 2 Telsa unit).

Basic Neurosciences Program (Laboratories)

Laboratory of Central Nervous Systems Studies—

D. Carleton Gajdusek, M.D.

This laboratory is engaged in three studies: 1) The medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning. High incidence and other unusual foci of chronic CNS diseases, asthma, parasitic and viral diseases, congenital metabolic defects, atypical patterns of puberty and

aging, toxic and deficiency syndromes, and unusual behavior syndromes, where isolation or cultural stereotypy may restrict variables and thus contribute to epidemiologic solutions, are under study. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photography and sound recording. New methods of handling such data for research are developed. 2) Slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents, and appear to cause autocatalytic formation and precipitation of amyloid fibers. The biological and molecular characterization of these unconventional viruses is the major focus of the work. 3) Aging of the brain, Alzheimer's, Pick's, Parkinson's, and Huntington's diseases, Down's syndrome, multiple sclerosis, amyotrophic lateral sclerosis, chronic epilepsies, and other diseases are intensively studied in molecular biological, microbiological, immunologic, genetic, and biochemical laboratories and clinics and in foci of high incidence throughout the world. We treat the aging and Alzheimer's disease problems as a problem of brain amyloidosis and study amyloid deposition at a molecular, cytochemical, and cell biological level. Biochemical and nucleating events triggered by CNS deposits of silicon, aluminum and calcium are also studied.

Within this framework intensive investigation of epidemic hemorrhagic fever/hemorrhagic fever with renal syndrome is being conducted on a worldwide basis on the isolation and characterization of the virus, its molecular nature and immunogenetics, its seroepidemiology, and the documentation of mild forms of the disease in man.

Laboratory of Viral and Molecular Pathogenesis—
M. Dubois-Dalcq, M.D.

This laboratory investigates the viral and molecular basis of nervous system diseases using the most advanced techniques of molecular and cell biology. The goals are to elucidate mechanisms of demyelination, dysmyelination, and remyelination with special attention to nervous system diseases caused by human retroviruses and papovaviruses. We analyze genetic mutation in viral host genes, identify their specific promoter-enhancer regions and transcription factors, and study the control of viral and host gene expression in transgenic mice. We investigate gene expression at the level of single nerve cells by *in situ* hybridization and triple label immunocytochemistry; we use purified nerve cells and immortalized cell lines to study growth and differentiation factors for nerve cells.

• Neural and Molecular Biology Section—
M. Dubois-Dalcq, M.D.

The section studies how neurotropic viruses enter the nervous system, express their genes, assemble their component and cause these cells to die or establish latency. Gene mutations causing dysmyelination in animals and men are being characterized. Precursor cells as well as the growth and regulatory factors essential to a normal myelination program during development and regeneration are studied *in vivo* and *in vitro*.

• Molecular Virology and Genetics Section—
G. Major, Ph.D.

The section studies human neurological diseases caused by neurotropic viruses. We analyze how viruses get disseminated from extraneural sites to the brain, how they interact with the immune system and which viral and cellular factors control gene expression in nerve cells. The section also studies human glial cell differentiation *in vitro*.

• Viral Pathogenesis Section—
H. Arnheiter, M.D.

Studies deal with the biological and molecular characterization of determinants of pathogenesis in viral and other diseases. Particular genes of the host of viruses are expressed in tissue culture systems and in transgenic mice, and the regulation and biological effects of expression of these genes is

assessed. The development of murine models for neurotropic human retroviruses and neuroimmunological studies are included.

- **Viral Replication Section—**

Manfred Schubert, Ph.D.

The section focuses on replication and gene expression of enveloped RNA viruses and, in particular, negative strand viruses such as VSV. Additional work is performed on the pathogenesis of HTLV-1 and HIV induced neurological diseases with respect to virus binding and entry into human nerve cells via specific viral receptors as well as viral assembly and mechanisms leading to viral latency.

Laboratory of Neural Control—

Robert E. Burke, M.D.

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the CNS control of spinal cord motoneurons and in turn the control exerted by these cells on the muscle fibers innervated by them, 2) the organization of information-processing systems in the spinal cord, and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computeroriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—

Harold Gainer, Ph.D.

Research is conducted on molecular events that underlie the normal functioning of the adult and developing nervous system and derangements that occur in neurologic diseases.

- Section on Cellular and Developmental Neurobiology—
Harold Gainer, Ph.D.

This section studies the development, molecular organization, and functional interactions of peptidergic neurons in the central nervous system. These include oxytocin, vasopressin, corticotrophin releasing factor, and gonadotrophin releasing factor (LHRH) neurons. In addition, the section studies various cytoskeletal proteins (neurofilaments and microtubule associated proteins) and enzymes (protein kinases) and their role in neuronal structure and function. Experimental models include intact rats and mice, dissociated and organotypic tissue culture systems, and the developing *Xenopus* embryo. Methods employed include light and electronmicroscopic immunocytochemistry, intracellular injection and electrical recording, monoclonal antibodies, and recombinant DNA techniques.

- Section on Enzyme Chemistry—
R. Wayne Albers, Ph.D.

This section is investigating the structure, mechanism, and regulation of membrane transport proteins with primary emphasis on the ATP-dependent sodium pump. Other projects encompass the characterization of Ca^{++} and Na^{+} and proton pumps and antiporters in excitable tissues.

Laboratory of Neural Control—

Andrew Zalewski, Ph.D.

This laboratory conducts research on regeneration and repair of nerve cells in damaged parts of the brain, spinal cord, and peripheral nervous system. Laboratory scientists study spontaneous regeneration of neurons as well as regeneration encouraged by nerve tissue implants. To study these problems, investigators use a variety of methods from histology, biochemistry, immunology, neurophysiology, and behavioral science.

- Neuronal Development and Regeneration Section—
Andrew Zalewski, Ph.D.

This section investigates the immunological factors that cause rejection of foreign nerve tissue grafts used to repair injured nerve tissue. Ways to promote the survival of nerve tissue grafts is also studied by altering graft antigenicity before transplant or by inducing immunosuppression in the host.

Laboratory of Neuropathology and Neuroanatomical Sciences—

Igor Klatzo, M.D.

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system.

- **Section on Cerebrovascular Pathology—**

Igor Klatzo, M.D.

Research is conducted on various aspects of pathophysiology of cerebral ischemia and brain edema. Elucidation of the pathomechanisms involved is attempted by evaluation and correlation of various parameters, such as changes in blood flow, electrical impedance, water content, electrolytes, glucose metabolism, behavior of the blood-brain barrier, immunohistochemical and morphological alterations on light microscopic and ultrastructural level in various models of ischemia and brain edema.

- **Section on Neurocytobiology—**

Maria Spatz, M.D.

This section investigates mechanisms involved in the development of cerebral ischemia, edema and EAE. Research is designed to elucidate the properties of the cerebral microvascular compartment as it relates to the function of the blood-brain barrier and cerebral blood flow under normal and pathological conditions. Specific studies include: 1) the interaction between various cellular elements of the microvessels and the glia, and 2) the interaction between cerebral microvascular endothelial cells and immune cells.

Laboratory of Experimental Neuropathology—

Henry deF. Webster, M.D.

This laboratory studies molecular and cellular mechanisms of myelin formation, maintenance and breakdown with special emphasis on the roles viruses may have in multiple sclerosis and other demyelinating diseases. The roles of gangliosides and protein phosphorylation in neuronal functions also are

being investigated. Virological, immunocytochemical, immunological, biochemical and biophysical techniques are being used in current projects.

Laboratory of Neurobiology—

Thomas S. Reese, M.D.

Conducts structural research on the organization of the nervous system. Specific cell biological problems are synaptic transmission, glial function, axoplasmic transport, organization of glial and neural membranes, and the intracellular sequestration of ions. The principal organizational problems investigated are the blood-brain barrier, and neural development and regeneration. Structural tools used are electron-microscopy, X-ray spectroscopy, immunocytochemistry, cryotechniques, and computer processed imaging.

- **Section on Functional Neuroanatomy—**

Thomas S. Reese, M.D.

This section is primarily concerned with studies on synaptic structure and function, redistribution of elements during neuronal activity and secretion, intrinsic membrane proteins and lipids, and neuronal cytoskeleton. Using modern electron optical and low temperature techniques, the structure of neural cells and membranes is investigated in close to molecular level of resolution.

- **Section on Structural Plasticity—**

Milton W. Brightman, Ph.D.

The section is engaged in studies to delineate the conditions necessary for the placement, survival, regeneration, and function of transplanted neurons—both peripheral and central, to characterize further the tropism between central and peripheral neurons and to analyze the structural changes in astrocytic cell membranes during degeneration and regeneration.

Laboratory of Neurophysiology—

Jeffery L. Barker, M.D.

All of the laboratory's projects involve multi-disciplinary analysis of the physiological properties of vertebrate central neurons studied *in vitro*. The techniques utilized encompass many of those current in cellular neurobiology, including electrophysiology, immunohistochemistry, electronmicroscopy,

flow cytometry and dissociated cell culture. A principal line of investigation is focused on the physiological properties of neurons cultured from different parts of the mammalian CNS, since monolayer cultures allow immediate accessibility to quantitative analysis of neuronal function at the cellular level. Using such a strategy, members of the laboratory are studying which properties are resident in different types of nerve cells, how these properties evolve during embryonic development, and what roles they play in intercellular communication. These studies are thus aimed at providing insight primarily into the question of what types of phenotypic properties are expressed by different CNS cells and secondarily into the related problem of how these properties differentiate the functions of one cell type from another. One long-term goal of the laboratory is a better understanding of the relationship between the activity of ion channels in neuronal membranes and the synthesis and secretion of specific transmitter substances.

Another area of considerable activity in the laboratory involves pharmacological experiments on the cellular mechanisms of actions of clinically important drugs like benzodiazepines, barbiturates, and convulsants using electrophysiological recording techniques (voltage-clamp and patch-clamp).

Laboratory of Molecular Biology—

Ernst Freese, Ph.D.

Development, differentiation, and cellular function are studied in a variety of cell types, especially those of the mammalian brain. Biochemical, immunochemical, and molecular genetic techniques are employed. Developmental effects of mutations and drugs are examined and related to hereditary and environmentally caused diseases.

- **Section on Developmental Biology—**

Ernst Freese, Ph.D.

Genomic DNA, its mutation and footprinting are studied to determine the mechanisms controlling transcription in different cell types, and cDNA in plasmids is used to transfect cells and oocytes for drug investigations. Changes in gene expression are analyzed during development, during neuron-astrocyte interactions, in animal models, and in human diseases. The genetic

structure and control of enzymes and receptors concerned with amino acid and other neurotransmitters in brain cells is under investigation.

- Section on Molecular Neurobiology—
Richard C. Henneberry, Ph.D.

Studies are designed to elucidate the mechanisms by which individual cells derived from the mammalian brain, perceive and respond to extracellular signals. Cell surface receptors for hormones and neurotransmitters, in particular those which function through modulation of cyclic nucleotide levels, are investigated using the methods of cell biology, biochemistry, and molecular biology. The roles of neurotransmitter receptors in the etiology of neurodegenerative diseases are studied.

- Laboratory of Biophysics—**
William J. Adelman, Jr., Ph.D.

Studies are under way on molecular, single-channel, and cellular mechanisms of excitation and ion conductance; membrane potentials and currents; generation of nerve and muscle impulses; synaptic activity; structural and chemical basis for axoplasmic and neuroplasmic transport; the biophysical basis for the functioning of simple nervous systems; biophysical neuropharmacology and molecular basis for rhythmic and spontaneous activity in neurones and skeletal and cardiac muscle. Such studies utilize physical and chemical techniques, digital computers, electron and light microscopy, and a variety of applied mathematical methods.

- Laboratory of Molecular and Cellular Neurobiology—**
The Laboratory of Molecular and Cellular Neurobiology takes a multidisciplinary approach to fundamental questions of neuroscience including the nature of memory; the molecular basis of demyelinating disease; the structure and regulation, both genetically and metabolically, of neurotransmitter receptors and their associated signal transducers in neural membranes.

- Membrane Biochemistry Section—
Peter Fishman, Ph.D.

The membrane biochemistry section is investigating the structure, biosynthesis and regulation of cell membrane components involved in various recognition phenomena and in

cellular signalling. These include: 1) complex glycoconjugates such as gangliosides which function as membrane receptors for certain toxins and viruses and as regulators of signals for cell growth and differentiation; and 2) the receptor-coupled adenylate cyclase and phospholipase C systems which mediate the cellular responses to various hormones, neurotransmitters and growth factors. Of particular interest are the complex mechanisms by which cells regulate their responses to external stimuli. These include up- and down-regulation of receptors, desensitization of receptor-effector coupling and cross-talk between different signal transduction systems.

- Neural Systems Section—

Daniel L. Alkon, M.D.

The section on neural systems studies how information is stored during associative learning and how it is made available for later recall. Biophysical and molecular mechanisms of associative learning are being analyzed in parallel for a mollusc (the sea snail *Hermisenda*) and a mammal (the rabbit). Parallel analyses offer the opportunity to uncover general cellular principals of learning and memory—principles which have been conserved over the course of evolution and which therefore could have relevance for human cognition. Parallel analyses also permit exploitation of critical experimental advantages unique to these two species. For *Hermisenda* it has been possible to demonstrate the first causal relationship of biophysical and molecular transformations within individual neurons to Pavlovian conditioning of a living animal. Biophysical transformations and molecular regulation which are common to both mollusc and mammal is studied.

- Receptor Biochemistry and Molecular Biology Section—

J. Craig Venter, Ph.D.

The section of receptor biochemistry and molecular biology key areas of investigation include 1) the molecular biology of neurotransmitter receptors; 2) the expression and site directed mutagenesis of neurotransmitter receptor genes; and 3) large scale DNA sequencing of neurotransmitter receptor genes and human chromosomal regions to which neurological disorders with a genetic basis have been mapped.

The neurotransmitter receptors under study in the section include muscarinic cholinergic, alpha- and beta-adrenergic, nicotinic and GABA_A/benzodiazepine, octopamine and dopamine receptors. The cloning and sequencing of genes encoding neurotransmitter receptors have revealed the existence of several gene families containing related receptor proteins. One of these families contains receptors that mediate the actions of hormones and neurotransmitters by guanine nucleotide regulatory proteins.

To examine the functional significance of single amino acids in more detail, other studies focus on site-directed mutagenesis of neurotransmitter receptors.

- Myelin and Brain Development Section—

Richard H. Quarles, Ph.D.

The section on myelin and brain development investigates the biochemistry of myeline and other membranes in the nervous system. Emphasis is placed on glycoconjugates such as the myelin-associated glycoprotein (MAG) which is in the immunoglobulin gene superfamily and appears to function in the interaction between myelin-forming cells and axons. Dysmyelinating mutants and neural tissue culture systems are utilized to determine the molecular mechanisms by which MAG functions during myelinogenesis. The roles of MAG and other glycoconjugates in the molecular pathogenesis of a variety of neurological diseases including multiple sclerosis are also under investigation. Serum antibodies to MAG and gangliosides that occur in patients with peripheral neuropathy are studied with regard to their specificity and pathogenic significance.

The Clinical Center

John L. Decker, M.D.
Director

Department of Transfusion Medicine

Harvey G. Klein, M.D.
Staff Fellowship

The Department of Transfusion Medicine accepts applications for a fellowship program in blood banking and immunohematology that is accredited by the Council on Graduate Medical Education. The fellowship assignment is usually for two years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is required.

The program offers specialized training for the hematologist and clinical pathologist in a patient-oriented transfusion program. The fellow receives broad experience in all aspects of transfusion medicine, including clinical and laboratory immunohematology, apheresis techniques, tissue typing, donor recruitment, and blood component preparation and therapy. The fellow participates actively in the service and teaching functions of the department.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Department of Transfusion Medicine provides an unique opportunity for collaborative research with the various institutes. Current programs include investigations of transfusion-transmitted viral disease, development and evaluation of innovative techniques for blood cell collection and separation, and applications of cellular radiolabeling techniques to studies of platelet preservation, platelet kinetics, red cell compatibility, and leukocyte kinetics.

Prospective applicants desiring more information should write to Richard J. Davey, M.D., Program Director, Department of Transfusion Medicine, Building 10, Room 5D56, National Institutes of Health, Bethesda, Maryland 20892.

Clinical Pathology Department

Ronald J. Elin, M.D., Ph.D.

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the institutes. The department is organized into four services: clinical chemistry, hematology, immunology, and microbiology.

In addition, there is a close working relationship with the Information Systems Management Department. The Clinical Chemistry, Hematology, Immunology, and Microbiology Services and the Information Systems Management Department, offer medical staff fellow positions, but not necessarily on a yearly basis.

- Clinical Chemistry—

Ronald J. Elin, M.D., Ph.D.

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of five individuals with M.D. and/or Ph.D. degrees. Approximately 260,000 tests are performed per month by a technical staff of 45 medical technologists, chemists, technicians, and medical aids. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of immunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference, range, instrument evaluation, and automated assay.

A medical staff fellow entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, immunoassay, urinalysis, special chemistry, and SMAC. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The fellow would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the fellow would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the fellow would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Medical Staff Fellow Program should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 2C407, National Institutes of Health, Bethesda, Maryland 20892.

- Hematology—

Harvey R. Gralnick, M.D.

The Hematology Service provides clinical and research experience in hematology. We have an active clinical and consultative service. The Hematology Service also has a research program directed at clinical and basic problems in Hematology. The service is responsible for the operation of the routine clinical hematology laboratories. Basic research projects include characterization of blood coagulation proteins, studies of the interactions of coagulation proteins and platelets and characterization of coagulation protein binding to platelets. Monoclonal antibodies have been developed against plasma and platelet coagulation factors. Other research endeavors include the use of immunologic and biochemical markers for platelet activation, the utilization of flow cytometry and the development of other procedures for detecting platelet activation.

The Hematology Service recruits medical staff fellows for a minimum of 2 years. The fellows will spend 6 months doing primarily clinical work. During this time, the fellow will also have the opportunity to develop a specific interest in investigative studies. Fellows will be encouraged to choose a problem for investigation which can be pursued with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Medical staff fellows whose primary interest is basic or laboratory research are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, these fellows will devote most of their time to laboratory research. The candidate who is chosen will be given an opportunity to choose an area of investigation, and a senior staff member will serve as his or her preceptor.

Any candidate interested in either program should send a letter indicating specific interests and a curriculum vitae to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 2C390, National Institutes of Health, Bethesda, Maryland 20892.

- Immunology—

Thomas A. Fleisher, M.D.

The immunology service provides training in various aspects of clinical diagnostic immunology as well as the opportunity to

participate in developmental and clinical pathologic research projects. The training program is primarily laboratory based but there is opportunity for considerable interaction with patient care physicians in allergy, immunology, and rheumatology (as well as other specialties). A medical staff fellow entering this program would develop broad-based knowledge in serologic, complement, immunoglobulin, electrophoresis and ELISA tests. In addition, the medical staff fellow would be involved in analytical two-color flow cytometry. The Immunology Service has tissue culture facilities which are available to support research protocols. The fellow will be expected to undertake either a developmental research project or clinicopathologic studies.

Persons interested in a medical staff fellowship position with the Immunology Service should contact Thomas A. Fleisher, M.D., Chief, Immunology Service, Clinical Pathology Department, Building 10, Room 2C410, National Institutes of Health, Bethesda, Maryland 20892.

- Microbiology—

James D. MacLowry, M.D.

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training programs is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, evaluation of automated reading devices for identifying bacteria, and the evaluation of new methodologies for antibiotic sensitivity testing. A variety of clinicopathologic studies is also undertaken or could be initiated under senior staff supervision.

Persons interested in a medical staff fellowship position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 2C385, National Institutes of Health, Bethesda, Maryland 20892.

- Laboratory Computer—
Thomas L. Lewis, M.D.

The Information Systems Management Department provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes physicians, statisticians, programmers, and computer operators. In addition to its own patient care computer systems, the service makes extensive use of the NIH IBM 3090 and DEC-10 time-sharing computers. Investigators in the service utilize extensive machine-readable files of clinical and laboratory information pertaining to NIH patients.

A medical staff fellow works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Fellows are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department. Appointments are for a period of 2 years and are not made yearly.

Interested candidates should write to Thomas L. Lewis, M.D., Associate Director for Information Systems Management, Clinical Center, Building 10, Room 2C137, National Institutes of Health, Bethesda, Maryland 20892.

Critical Care Medicine Department

Henry Masur, M.D.

The Critical Care Medicine Department is offering 2- to 3-year fellowships in critical care medicine. To be eligible, a physician must have completed 3 years of residency in internal medicine, anesthesiology, or general surgery. The fellowship consists of a first year of clinical training in critical care medicine in the intensive care units at the National Institutes of Health and in the medical-surgical intensive care unit at a major regional trauma center. The clinical training provides

broad experience in the care of critically ill patients and in a wide variety of procedures necessary to critical care. The second year (and an optional third year for selected fellows) consists of an individually designed program in clinical investigation or basic laboratory research related to critical illnesses. The NIH Fellowship Program is designed to satisfy all the subspecialty Board requirements for critical care medicine. Critical Care Medicine Boards were held for the first time in 1987.

The fellowship program is designed to provide excellent clinical training in the care of extraordinarily sick patients with multisystem organ dysfunction. Critical care physicians in the NIH ICU have primary responsibility for care of the patient. The critical care physicians work closely with referring physicians and call on multiple consultative services necessary to give full intensive care to these patients. The Critical Care Medicine Department consists of a senior staff that has subspecialty training in cardiology, pulmonary diseases, anesthesiology, infectious diseases, and critical care medicine. The staff performs most of the invasive procedures (Swan Ganz catheterization, cardiac catheterization, bronchoscopy, etc.) themselves in a specially constructed procedure/catheterization laboratory in the ICU. The ICU also has capability for computer processing and analysis, noninvasive (echocardiography, nuclear scanning) cardiac diagnostic studies, and pulmonary function studies.

The fellowship research training is designed to produce independent clinical investigators in the field of critical care medicine. The educational program includes weekly conferences on clinical critical care medicine and seminars regarding ongoing research programs in the department. Each fellow will have a senior staff member guiding the investigations. Ongoing research in the department includes the following: studies of hemodynamics and cardiovascular function in different forms of shock; the immunopathogenesis of septic shock; capillary leak syndromes; pulmonary functional abnormalities in shock lung; studies of immune cellular function in shock lung, asthma, and other forms of severe pulmonary disease; critical care of the immunocompromised host; and studies of immune cellular function and therapy of the acquired immune deficiency syndrome (AIDS).

Applications must be completed by November 10, nineteen months prior to the anticipated start of the fellowship. For further information on the program, please contact Henry Masur, M.D., Chief, Critical Care Medicine Department, Building 10, Room 10D48, National Institutes of Health, Bethesda, Maryland 20892.

Nuclear Medicine Department

Ronald D. Neumann, M.D.

Residency Training

The American Accreditation Council for Graduate Medical Education has approved the Nuclear Medicine Department for a 2-year residency training program in nuclear medicine. Prerequisites for applicants include graduation from a medical school approved by the Liaison Committee on Medical Education and at least two years of preparatory training in a residency program in the U.S.A. approved by the Accreditation Council for Graduate Medical Education.

Residents accepted into the NIH Nuclear Medicine Program will attend a 2 month basic nuclear sciences course at the Bethesda Naval Hospital and a 3 month rotation at George Washington University Hospital and Children's Hospital in addition to training at the Clinical Center.

The training experience at NIH will include diagnostic and therapeutic nuclear medicine procedures, PET imaging, radiopharmaceutical preparation, applied physics, data processing, and research training. Many clinical and research programs of the Nuclear Medicine Department collaborate with physicians and scientists from the various NIH Institutes.

Bioethics Program

Alison Wichman, M.D.

Staff Fellowship

The Bioethics Program accepts applications for a one year fellowship in applied clinical and research bioethics. Applicants must have completed an accredited residency program and express a strong interest in the practice of clinical bioethics.

The fellowship includes experiences in clinical bioethics consultation, research protocol review with emphasis on protection of research subjects and informed consent, policy evaluation and formulation in a large tertiary care research center, Institutional Review Board experience, multidisciplinary

bioethics teaching experience, research in bioethical issues, and participation in publication of research endeavors.

The fellowship is designed to meet the specific needs of each candidate, but is designed to give a grounding in the basic didactic elements of medical ethics and research and clinical bioethics. The study course will be determined cooperatively by the Bioethics Program director and the fellow.

For further information and application procedures, contact Alison Wichman, M.D., Chief, Bioethics Program, Clinical Center, Building 10, Room 1C116, NIH, 9000 Rockville Pike, Bethesda, MD 20892 or call 301-496-2429.

Arnold W. Pratt, M.D.

Director

The Laboratory of Applied Studies, DCRT, offers 2- to 3-year medical staff fellowship positions to physicians with additional training in physical science, engineering, and/or mathematics and statistics; 2 or more years training or experience with computers including programming; and at least 1 year of residency (internship).

Laboratory of Applied Studies—

James E. Fletcher, Ph.D., Chief

This laboratory engages in independent and collaborative research on innovative applications of mathematics, computer science, and engineering to problems of clinical medicine and basic biology. The senior staff includes mathematicians, physicians, electronics engineers, and computer systems analysts; and facilities include access to micro-, mini-, and main frame computer systems (i.e., IBM-PC's, DEC systems, Apple MacIntosh, IBM 3090 vector facilities, and super computers CRAY, STAR, etc.).

The fellow will collaborate with clinicians or bench lab scientists in one or more of such current projects as: 1) biological signal analysis, e.g., evaluating electrophysiologic responses to changes in autonomic tone, cardiotoxic drugs and infective myocarditis; 2) analysis of multimodality images to correlate structure and function, e.g., echocardiology, PET scans, single photon tomography, 3D visualization, and pattern recognition; 3) development of mathematical modeling tools and database analysis algorithms, e.g., spatial and temporal representation of laboratory acquired data, models and analysis of receptor binding and reaction-diffusion kinetics, and the development of predictive simulation models for mammalian immune systems or other physiologic systems of current interest.

The fellow will be guided by the senior staff, especially in such areas as: modeling of physiologic processes, mathematical methodology, signal analysis, image processing, and computer automation.

Interested candidates should contact: James J. Bailey, M.D.,
DCRT, Building 12A, Room 2041, National Institutes of
Health, Bethesda, Maryland 20892.

Academic Programs Available to Medical Staff Fellows

Among the academic programs open to an NIH medical staff fellow are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc. (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 40 to 50 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the FAES Graduate School, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The FAES is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters, fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: Biochemistry and Biophysics, Biology and Genetics, Chemistry and Physics, General Studies, Languages, Mathematics and Computer Science, Medicine and Physiology, Microbiology and Immunology, Pharmacology and Toxicology, Psychiatry and Psychology, and Statistics. In addition, Medical Subspeciality Board Review Courses are offered in Endocrinology and Metabolism, Medical Oncology, Internal Medicine, Infectious Diseases and Clinical Genetics. A series of daytime biotechnology training courses are offered by the Graduate School on a contractual basis, and include both lecture and laboratory sessions.

Further inquiries regarding the Graduate School and requests for its current catalog should be directed to: Registrar, Foundation for Advanced Education in the Sciences, Inc., Graduate School, One Cloister Court, Bethesda, Maryland 20814-1460.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is

conducted by one of the institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff and serve to keep individual investigators abreast of current emphasis in all clinical research.

**Topics Presented in the
1988-1989 Series Were:**

October 26, 1988

Samuel Broder, M.D.

Antiretroviral Therapy in AIDS

November 30, 1988

Henry Masur, M.D.

Pneumocystis Pneumonia

December 21, 1988

Thomas Waldmann, M.D.

*The Multi-Chain Interleukin-2 Receptor: A Target for
Immunotherapy*

January 25, 1989

Joseph Parrillo, M.D.

Cardiovascular Dysfunction in Human Septic Shock

February 22, 1989

Michael Frank, M.D.

*The Angioedema Syndromes: Diagnosis, Pathophysiology, and
Treatment*

April 5, 1989

John Mulvihill, M.D.

Neurofibromatosis: 1989 Update

April 26, 1989

Judith Rapoport, M.D.

Obsessive-Compulsive Behavior

May 24, 1989

Jay Hoofnagle, M.D.

Non-A, Non-B Hepatitis

Several formal lectures are presented annually. **The National Institute of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the institutes. Dr. Thomas R. Cech of the Howard Hughes Medical Institute, University of Colorado, gave the most recent NIH lecture in November 1988 on "RNA as an Enzyme."

The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-1950, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Marian Elliott Koshland of the University of California at Berkeley presented the 1988 Dyer lecture on "Mechanism of Peptide Hormone Signalling: An Immunoglobulin Gene Model." Among other distinguished speakers have been Nobel laureates Dr. Howard M. Temin, who spoke on "The Replication and Possible Origin of RNA Viruses with a DNA Polymerase," and Dr. D. Carleton Gajdusek, who discussed his work on kuru.

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1988

George R. Martin, Ph.D.

Basement Membranes: Key Determinants of Differentiation and Their Role in Cancer Metastasis

1987

Igor Dawid, Ph.D.

Molecular Embryology: New Approaches to Old Questions

1985

Edward Korn, Ph.D.

Biochemical Regulation of Actomyosin-Dependent Cell Motility

1984

George Khoury, M.D.

Enhancers: Regulatory Elements in Eukaryotic Gene Expression

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional educational opportunities. Some medical staff fellows augment their experience at NIH with studies at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open-stack, self-service library with a collection of some 272,000 volumes of medical and scientific books and journals. Some 2,000 new books and 3,700 journal subscriptions are received annually. An integral part of the research needs of the NIH staff, the NIH library's major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation, and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs, and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 3 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the

library's computerized database of journal references (MEDLINE) is available both at NLM and at the NIH library.

Abnormalities

- Human Genetics Branch (NICHD), 138-140
- Laboratory of Developmental Biology and Anomalies (NIDR), 162-163, 198-199
- Laboratory of Developmental Pharmacology (NICHD), 148-149, 196
- Laboratory of Reproductive and Developmental Toxicology (NIEHS), 216-217

Acquired Immunodeficiency Syndrome

- Laboratory of Immunoregulation (NIAID), 101-103, 184
- Laboratory of Tumor Cell Biology (NCI), 45-47

Aging

- see also** National Institute on Aging (NIA)
- Clinical Investigations and Patient Care Branch (NIDR), 160

AIDS

- see** Acquired Immunodeficiency Syndrome

Alcoholism

- see** National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Allergy

- see** Hypersensitivity

Anesthesiology

- Neurobiology and Anesthesiology Branch (NIDR), 158-159, 164-165, 198

Arthritis

- see** National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Behavior

- Biological Psychiatry Branch (NIMH), 232-233, 241-244
- Child Psychiatry Branch (NIMH), 256
- Laboratory of Behavioral and Neurological Toxicology (NIEHS), 217
- Laboratory of Behavioral Sciences (NIA), 86-87
- Laboratory of Comparative Ethology (NICHD), 140-142

Laboratory of Developmental Neurobiology (NICHD), 142-145,
196-197, 197-198

Laboratory of Developmental Psychology (NIMH), 258

Biochemistry

Bone Research Branch (NIDR), 162

Clinical Investigations and Patient Care Branch (NIDR), 160,
161-162

Developmental and Metabolic Neurology Branch (NINDS),
269-270

Endocrinology and Reproduction Research Branch (NICHD),
152-154, 193-194

Genetics and Biochemistry Branch (NIDDK), 122-123

Laboratory of Biochemical Genetics (NHLBI), 72-73, 222-223

Laboratory of Biochemical Pharmacology (NCI), 57, 189-190

Laboratory of Biochemical Pharmacology (NIDDK), 126, 213-214

Laboratory of Biochemical Risk Analysis (NIEHS), 175

Laboratory of Biochemistry (NCI), 23-25

Laboratory of Biochemistry (NHLBI), 73-74

Laboratory of Biochemistry and Metabolism (NIDDK), 127,
204-205

Laboratory of Biological Chemistry (NCI), 56-57, 187-188

Laboratory of Biological Chemistry (NIA), 89-90

Laboratory of Cerebral Metabolism (NIMH), 226-227, 259-260

Laboratory of Chemical Biology (NIDDK), 123, 128, 209

Laboratory of Developmental Neurobiology (NICHD), 142-145,
196-197, 197-198

Laboratory of General and Comparative Biochemistry (NIMH),
259

Laboratory of Genetics (NIEHS), 173

Laboratory of Neurochemistry (NIMH), 227, 260

Laboratory of Neurochemistry (NINDS), 237, 278-279

Laboratory of Preclinical Pharmacology (NIMH), 234, 265

Molecular Disease Branch (NHLBI), 71

Bioethics

staff fellowship (CC), 292-293

Biology

see also Microbiology

Biological Resources Branch (NIAID), 110-111

Bone Research Branch (NIDR), 162
 Cell Biology and Metabolism Branch (NICHD), 154-156, 195
 Clinical Investigations and Patient Care Branch (NIDR), 160,
 161-162
 Division of Cancer Biology and Diagnosis (NCI), 15
 Genetics and Biochemistry Branch (NIDDK), 122-123, 200
 Human Genetics Branch (NICHD), 138-140
 Laboratory of Cell Biology (NCI), 25
 Laboratory of Cell Biology (NHLBI), 75-76, 222
 Laboratory of Cell Biology (NIMH), 225-226, 258
 Laboratory of Cell Biology and Genetics (NIDDK), 130, 206
 Laboratory of Cellular Development and Oncology (NIDR), 161
 Laboratory of Cellular and Developmental Biology (NIDDK), 131,
 210-211
 Laboratory of Cellular and Molecular Biology (NCI), 39
 Laboratory of Cellular and Molecular Biology (NIA), 90-91
 Laboratory of Chemical Biology (NIDDK), 128, 209
 Laboratory of Developmental Biology and Anomalies (NIDR),
 162-163, 198-199
 Laboratory of Developmental and Molecular Immunity (NICHD),
 149-150
 Laboratory of Developmental Neurobiology (NICHD), 142-145,
 196-197, 197-198
 Laboratory of Immunobiology (NCI), 26
 Laboratory of Mathematical Biology (NCI), 29-31, 193
 Laboratory of Metabolism and Molecular Biology (NIAAA), 94,
 96-97
 Laboratory of Molecular and Cellular Biology (NIDDK), 200-201
 Laboratory of Molecular and Cellular Neurobiology (NINDS),
 283-285
 Laboratory of Molecular and Developmental Biology (NEI), 62-63
 Laboratory of Molecular Biology (NCI), 26-28, 190-191
 Laboratory of Molecular Biology (NIDDK), 130-131, 203
 Laboratory of Molecular Biology (NIMH), 227-228
 Laboratory of Molecular Biology (NINDS), 282-283
 Laboratory of Molecular Biophysics (NIEHS), 172, 215-216
 Laboratory of Molecular Genetics (NIA), 89
 Laboratory of Molecular Genetics (NICHD), 145-147
 Laboratory of Pathobiology (NIAID), 113-114
 Laboratory of Physical Biology (NIAMS), 168
 Laboratory of Pulmonary Pathobiology (NIEHS), 172, 217-218

Laboratory of Retinal Cell and Molecular Biology (NEI), 60-61
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197
Laboratory of Tumor Cell Biology (NCI), 45-47
Laboratory of Tumor Immunology and Biology (NCI), 32-35

Biometry

Biometry and Epidemiology Program (NEI), 59-60
Division of Biometry and Risk Assessment (NIEHS), 173-175
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197

Biophysics

Bone Research Branch (NIDR), 162
Laboratory of Biophysics (NINDS), 283
Laboratory of Developmental Neurobiology (NICHD), 142-145,
196-197, 197-198
Laboratory of Molecular Biophysics (NIEHS), 172, 215-216
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197

Blood Banking

see Transfusion Medicine

Cancer

see Oncology

Cardiology

see also National Heart, Lung and Blood Institute (NHLBI)
Laboratory of Cardiovascular Sciences (NIA), 88-89

Cell Biology

see Biology

Chemistry

see also Biochemistry
Bone Research Branch (NIDR), 162
clinical chemistry, credit towards board certification in, 7
clinical chemistry, fellowships in, 287
Laboratory of Bioorganic Chemistry (NIDDK), 127-128, 202
Laboratory of Chemical Biology (NIDDK), 123, 128, 209

Laboratory of Chemical Pharmacology (NHLBI), 77-79, 220-221
Laboratory of Chemical Physics (NIDDK), 129, 203
Laboratory of Chemistry (NHLBI), 79-80
Laboratory of Chemistry (NIDDK), 129-130
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197

Clinical Center

see Warren Grant Magnuson Clinical Center (CC)

Clinical Pathology

see Pathology

Communication Disorders

see National Institute on Deafness and Other Communication
Disorders (NIDCD)

Computers

Computer Technology Branch (NIEHS), 175
fellowships in laboratory computer service, 6
Laboratory of Applied Studies (DCRT), 294-295
Laboratory Computer Service of Clinical Pathology Department
(CC), 290
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197
Medical Information System (CC), 2

Conferences

see Seminars and Lectures

Critical Care

credit towards board certification in, 7
Critical Care Medicine Department (CC), 3, 290-292
fellowships in, 3

Deafness

see National Institute on Deafness and Other Communication
Disorders (NIDCD)

Dentistry

see National Institute of Dental Research (NIDR)

Dermatology

see also National Institute of Arthritis and Musculoskeletal and
Skin Diseases (NIAMS)
credit towards board certification in, 7
Dermatology Branch (NCI), 15

Development

see Growth and Development

Diabetes Mellitus

see also National Institute of Diabetes and Digestive and Kidney
Diseases (NIDDK)
Laboratory of Clinical Physiology (NIA), 85

Digestive Diseases

see Gastroenterology

Division of Computer Research and Technology (DCRT)

Laboratory of Applied Studies, 294-295

Drugs

see Pharmacology

Embryology

see Growth and Development

Endocrinology

board examinations, 9
Clinical Endocrinology Branch (NIDDK), 118-119, 206-207
credit towards board certification in, 7
Developmental and Metabolic Neurology Branch (NINDS),
269-270
Developmental Endocrinology Branch (NICHD), 8, 136-138
Endocrinology and Reproduction Research Branch (NICHD),
152-154, 193-194
Endocrinology Fellowship program (CC), 8-9
board examinations, 9
lectures and courses, 9
medical student program, 9
Hypertension-Endocrine Branch (NHLBI), 70, 221-222
interinstitute endocrinology training program, 8-9, 68-69

Laboratory of Clinical Physiology (NIA), 85
Laboratory of Developmental Neurobiology (NICHD), 142-145,
196-197, 197-198
Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197
Metabolic Diseases Branch (NIDDK), 123-124, 205
Metabolism Branch (NCI), 15, 191
Molecular, Cellular and Nutritional Endocrinology Branch
(NIDDK), 119-120, 201-202
pediatric endocrinology, credit towards board certification in, 7
reproductive endocrinology, credit towards board certification
in, 8

Environmental Health

see also National Institute of Environmental Health Sciences
(NIEHS)
Environmental Epidemiology Branch (NCI), 47
Laboratory of Developmental Pharmacology (NICHD), 148-149,
196

Epidemiology

Biometry and Epidemiology Program (NEI), 59-60
Clinical Epidemiology Branch (NCI), 47-48
Environmental Epidemiology Branch (NCI), 47
Epidemiology and Biostatistics Program (NCI), 47
Epidemiology Branch (NIEHS), 175
Epidemiology and Oral Disease Prevention Program (NIDR),
159-160
Longitudinal Studies Branch (NIA), 85
Radiation Epidemiology Branch (NCI), 48

Epilepsy

see Neurology

Eye Diseases

see National Eye Institute (NEI)

Fellowships

see Medical Staff Fellowships

Foundation for Advanced Education in the Sciences (FAES)

evening courses available to staff fellows, 69, 136, 296

Gastroenterology

see also National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Clinical Investigations and Patient Care Branch (NIDR), 160, 161-162

credit towards board certification in, 7

Genetics

Biological Psychiatry Branch (NIMH), 232-233, 241-244

Genetics and Biochemistry Branch (NIDDK), 122-123, 200

Human Genetics Branch (NICHD), 138-140

Interinstitute Medical Genetics Program, 10-11, 135

Laboratory of Biochemical Genetics (NHLBI), 72-73, 222-223

Laboratory of Cell Biology and Genetics (NIDDK), 130, 206

Laboratory of Comparative Ethology (NICHD), 140-142

Laboratory of Developmental Neurobiology (NICHD), 142-145, 196-197, 197-198

Laboratory of Developmental Pharmacology (NICHD), 148-149, 196

Laboratory of Genetics (NIEHS), 173

Laboratory of Immunogenetics (NIAID), 105-106, 184

Laboratory of Mammalian Genes and Development (NICHD), 147-148

Laboratory of Molecular Carcinogenesis (NIEHS), 173

Laboratory of Molecular Genetics (NIA), 89

Laboratory of Molecular Genetics (NICHD), 145-147

Laboratory of Molecular Genetics (NIEHS), 173

medical and pediatric genetics, credit towards board certification in, 7

Gerontology

see National Institute on Aging (NIA)

Growth and Development

Bone Research Branch (NIDR), 162

Developmental and Metabolic Neurology Branch (NINDS), 269-270

Developmental Endocrinology Branch (NICHD), 8, 136-138

Human Genetics Branch (NICHD), 138-140
 Laboratory of Cellular and Developmental Biology (NIDDK), 131
 Laboratory of Comparative Ethology (NICHD), 140-142
 Laboratory of Developmental Biology and Anomalies (NIDR),
 162-163, 198-199
 Laboratory of Developmental and Molecular Immunity (NICHD),
 149-150
 Laboratory of Developmental Neurobiology (NICHD), 142-145,
 196-197, 197-198
 Laboratory of Developmental Pharmacology (NICHD), 148-149,
 196
 Laboratory of Mammalian Genes and Development (NICHD),
 147-148
 Laboratory of Molecular and Developmental Biology (NEI), 62-63
 Laboratory of Molecular Genetics (NICHD), 145-147
 Laboratory of Reproductive and Developmental Toxicology
 (NIEHS), 216-217
 Molecular, Cellular and Nutritional Endocrinology Branch
 (NIDDK), 119-120, 201-202

Gynecology and Obstetrics

Developmental Endocrinology Branch (NICHD), 8, 136-138
 Medicine Branch (NCI), 51-52
 reproductive endocrinology, credit towards board certification
 in, 8

Hearing

see National Institute on Deafness and Other Communication
 Disorders (NIDCD)

Hematology

see also Transfusion Medicine
 Clinical Hematology Branch (NHLBI), 70
 Clinical Hematology Branch (NIDDK), 120
 Clinical Pathology Department (CC), 3, 286-290
 credit towards board certification in, 7
 Laboratory of Molecular Hematology (NHLBI), 81, 219
 pediatric hematology, credit towards board certification in, 8
 Pediatric Oncology Branch (NCI), 53-54

Hypersensitivity

- approved residence training program in, 7
- credit towards board certification in, 7
- Laboratory of Clinical Investigation (NIAID), 99, 100-101, 183
- Laboratory of Developmental and Molecular Immunity (NICHHD), 149-150

Immunology

- approved residency training program in, 7
- Biological Resources Branch (NIAID), 110-111
- Human Genetics Branch (NICHHD), 138-140
- Immunology Branch (NCI), 15
- Immunology Service (CC), 288-289
- Laboratory of Cellular and Molecular Immunology (NIAID), 111-112
- Laboratory of Clinical Investigation (NIAID), 99, 100-101, 183
- Laboratory of Clinical Physiology (NIA), 85
- Laboratory of Developmental and Molecular Immunity (NICHHD), 149-150
- Laboratory of Immunobiology (NCI), 26
- Laboratory of Immunogenetics (NIAID), 105-106, 184
- Laboratory of Immunology (NEI), 63-64
- Laboratory of Immunology (NIAID), 106-107
- Laboratory of Immunology (NIDR), 163
- Laboratory of Immunopathology (NIAID), 109-110
- Laboratory of Immunoregulation (NIAID), 99-100, 101-103, 184
- Laboratory of Microbiology and Immunology (NIDR), 199-200
- Laboratory of Tumor Immunology and Biology (NCI), 32-35
- Metabolism Branch (NCI), 15, 191
- Neuroimmunology Branch (NINDS), 273
- Pediatric Oncology Branch (NCI), 53-54

Indians, North American

- study by Phoenix Clinical Research Section (NIDDK), 124-125
- study by Southwestern Field Studies Section (NIDDK), 125-126

Infant, Newborn

- see Pediatrics

Infectious Diseases

- see Microbiology

Instrumentation and Methodology

Laboratory of Technical Development (NHLBI), 81-82

Internal Medicine

board examinations, 9

credit towards board certification in (NHLBI), 7, 66-67

Kidney

see Urogenital System

Lectures

see Seminars and Lectures

Lung

see Respiratory System

Mathematics

Laboratory of Mathematical Biology (NCI), 29-31, 193

Laboratory of Theoretical and Physical Biology (NICHD),
150-152, 197

Mathematical Research Branch (NIDDK), 131-132

Statistics and Biomathematics Branch (NIEHS), 174-175

Medical Libraries

facilities available to staff fellows, 299-300

Medical Oncology

see Oncology

Medical Schools

in Washington-Baltimore area, 299

Medical Staff Fellowships

academic programs available to staff fellows, 296-300

combined clinical staff conferences and lectureships, 296-299

evening courses, 69, 136, 296

library facilities, 299-300

Washington-Baltimore educational complex, 299

application for, 12-14

approved training programs, 6-8

Bioethics Program (CC), 292-293

clinical research appointments:

- in NCI, 15
- in NHLBI, 66-67
- in NIAAA, 94
- in NIAMS, 166
- in NICHD, 134-135
- in NIDCD, 115
- in NIDDK, 116-117
- in NIMH, 239-240
- in NINDS, 266-267

dental staff fellows, 4, 157

employment benefits, 13

Endocrinology Fellowship Program (CC), 5, 8-9

foreign medical graduates, 12-13

general description, 3-4

in Clinical Oncology Program (NCI), 50-51

in Clinical Pathology Department (CC), 3, 286-290

in Critical Care Medicine Department (CC), 3, 290-292

in Department of Transfusion Medicine (CC), 3, 286

in epidemiology and clinical investigations in NIDDK, 118-126

in Laboratory of Applied Studies (DCRT), 294-295

in NEI, 59-65

in NIA, 83-84

in NIAID, 99

in NIDR, 157-158

in NIEHS, 169-170

in Nuclear Medicine Department (CC), 3, 292

in Pharmacology Research Associate Program of NIGMS, 5, 16,

68, 85, 95, 99, 117, 136, 158, 166, 170, 177-238, 267

in surgery in NHLBI, 67-68

Interinstitute Medical Genetics Program 10-11, 135

laboratory research appointments:

- in NCI, 16
- in NHLBI, 68
- in NIAAA, 94-95
- in NICHD, 135-136
- in NIDDK, 117
- in NIMH, 240
- in NINDS, 267

method of selection, 13-14

requirements for application, 12-14

Medical Students

- clinical electives for, 5-6
- participation in courses offered by Endocrinology Fellowship Program (CC), 9
- participation in Interinstitute Medical Genetics Program, 10-11

Metabolism and Nutrition

- Cell Biology and Metabolism Branch (NICHD), 154-156, 195
- Developmental and Metabolic Neurology Branch (NINDS), 269-270
- Human Genetics Branch (NICHD), 138-140
- Laboratory of Biochemistry and Metabolism (NIDDK), 127, 204-205
- Laboratory of Bioorganic Chemistry (NIDDK), 127-128, 202
- Laboratory of Cardiac Energetics (NHLBI), 74-75
- Laboratory of Cellular Metabolism (NHLBI), 76-77, 223-225
- Laboratory of Cerebral Metabolism (NIMH), 226-227, 259-260
- Laboratory of Clinical Physiology (NIA), 85
- Laboratory of Developmental Neurobiology (NICHD), 142-145, 196-197, 197-198
- Laboratory of Experimental Therapeutics and Metabolism (NCI), 186-187
- Laboratory of Kidney and Electrolyte Metabolism (NHLBI), 80
- Laboratory of Metabolism and Molecular Biology (NIAAA), 94, 96-97
- Laboratory of Theoretical and Physical Biology (NICHD), 150-152, 197
- Metabolic Diseases Branch (NIDDK), 123-124, 205
- Metabolism Branch (NCI), 15, 191
- Molecular, Cellular and Nutritional Endocrinology Branch (NIDDK), 119-120, 201-202
- Molecular Disease Branch (NHLBI), 71
- nutrition development programs in NIDDK, 117
- Phoenix Clinical Research Section (NIDDK), 124-125
- Southwestern Field Studies Section (NIDDK), 125-126

Microbiology

- see also** Acquired Immunodeficiency Syndrome
- Clinical Pathology Department (CC), 3, 286-290
- credit towards board certification in, 7
- fellowships in, 7, 289-290

infectious diseases, credit towards board certification in, 7
 Laboratory of Central Nervous System Studies (NINDS), 275-276
 Laboratory of Clinical Investigation (NIAID), 99, 100-101, 183
 Laboratory of Developmental and Molecular Immunity (NICHD),
 149-150
 Laboratory of Infectious Diseases (NIAID), 104-105
 Laboratory of Microbial Ecology (NIDR), 163-164
 Laboratory of Microbial Structure and Function (NIAID), 113
 Laboratory of Microbiology and Immunology (NIDR), 199-200
 Laboratory of Molecular Microbiology (NIAID), 108-109
 Laboratory of Molecular Virology (NCI), 43-44
 Laboratory of Parasitic Diseases (NIAID), 107-108
 Laboratory of Pathobiology (NIAID), 113-114
 Laboratory of Persistent Viral Diseases (NIAID), 112
 Laboratory of Tumor Virus Biology (NCI), 44, 189
 Laboratory of Viral Carcinogenesis (NCI), 44-45
 Laboratory of Viral Diseases (NIAID), 103-104, 184-185
 Laboratory of Viral and Molecular Pathogenesis (NINDS),
 277-278
 Pediatric Oncology Branch (NCI), 53-54
 Rocky Mountain Laboratories (NIAID), 112-114

Molecular Biology

see Biology

Musculoskeletal Diseases

see National Institute of Arthritis and Musculoskeletal and Skin
 Diseases (NIAMS)

Mutagenesis

Laboratory of Developmental Pharmacology (NICHD), 148-149,
 196
 Laboratory of Genetics (NIEHS), 173
 Laboratory of Molecular Genetics (NICHD), 145-147
 Molecular Modeling Section (NIEHS), 174
 Statistics and Biomathematics Branch (NIEHS), 174-175

National Cancer Institute (NCI)

appointments in clinical research, 15
 Dermatology Branch, 15
 Immunology Branch, 15

- Laboratory of Pathology, 15
- Metabolism Branch, 15, 191
- appointments in laboratory research, 16
- basic research laboratories of, 23-26
 - Laboratory of Biochemistry, 23-25
 - Laboratory of Cell Biology, 25
 - Laboratory of Cellular Oncology, 35-36
 - Laboratory of Genetics, 31-32
 - Laboratory of Immunobiology, 26
 - Laboratory of Mathematical Biology, 29-31, 193
 - Laboratory of Molecular Biology, 26-28, 190-191
 - Laboratory of Pathology, 28-29
 - Laboratory of Tumor Immunology and Biology, 32-35
- clinical research branches of, 16-23
 - Dermatology Branch, 16-17
 - Experimental Immunology Branch, 17-19
 - Immunology Branch, 20-21
 - Metabolism Branch, 21-23, 191
- Developmental Therapeutics Program, 56-58
 - Laboratory of Biochemical Pharmacology, 57, 189-190
 - Laboratory of Biological Chemistry, 56-57, 187-188
 - Laboratory of Molecular Pharmacology, 57-58
- medical staff fellows in, 56-58
- Division of Cancer Biology and Diagnosis, 15
- Division of Cancer Etiology, 36-48
 - Biostatistics Branch, 48
 - Clinical Epidemiology Branch, 47-48
 - Environmental Epidemiology Branch, 47
 - Epidemiology and Biostatistics Program, 47
 - Laboratory of Biology, 36-37
 - Laboratory of Cellular and Molecular Biology, 39
 - Laboratory of Cellular Carcinogenesis and Tumor Promotion, 40-41, 186
 - Laboratory of Comparative Carcinogenesis, 38-39
 - Laboratory of Experimental Carcinogenesis, 37-38, 192
 - Laboratory of Experimental Pathology, 41
 - Laboratory of Human Carcinogenesis, 42, 188
 - Laboratory of Molecular Oncology, 42-43
 - Laboratory of Molecular Virology, 43-44
 - Laboratory of Tumor Cell Biology, 45-47
 - Laboratory of Tumor Virus Biology, 44, 189

- Laboratory of Viral Carcinogenesis, 44-45
- Radiation Epidemiology Branch, 48
- Division of Cancer Treatment, 48-56
 - Cancer Therapy Evaluation Program, 48-49
 - Clinical Investigations Branch, 49
 - Clinical Oncology Program, 50-51
 - Investigational Drug Branch, 49-50
 - Medicine Branch, 51-52
 - NCI-Navy Medical Oncology Branch, 52-53
 - Pediatric Oncology Branch, 53-54
 - Radiation Oncology Branch, 54-55
 - Surgery Branch, 55
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 186-193
 - Clinical Pharmacology Branch, 190
 - Laboratory of Biochemical Pharmacology, 189-190
 - Laboratory of Biological Chemistry, 187-188
 - Laboratory of Cellular Carcinogenesis and Tumor Promotion, 186
 - Laboratory of Experimental Carcinogenesis, 192
 - Laboratory of Experimental Therapeutics and Metabolism, 186-187
 - Laboratory of Human Carcinogenesis, 188
 - Laboratory of Mathematical Biology, 193
 - Laboratory of Molecular Biology, 190-191
 - Laboratory of Tumor Virus Biology, 189
 - Metabolism Branch, 191

National Eye Institute (NEI)

- Biometry and Epidemiology Program, 59-60
- Clinical Branch, 64-65
- Laboratory of Immunology, 63-64
- Laboratory of Mechanisms of Ocular Disease, 61
- Laboratory of Molecular and Developmental Biology, 62-63
- Laboratory of Ophthalmic Pathology, 63
- Laboratory of Retinal Cell and Molecular Biology, 60-61
- Laboratory of Sensorimotor Research, 61-62

National Heart, Lung, and Blood Institute (NHLBI)

- appointments in clinical research, 66-67
- appointments in laboratory research, 68

- basic research laboratories of, 72-82
 - Laboratory of Biochemical Genetics, 72-73, 222-223
 - Laboratory of Biochemistry, 73-74, 219-220
 - Laboratory of Cardiac Energetics, 74-75
 - Laboratory of Cell Biology, 75-76, 222
 - Laboratory of Cellular Metabolism, 76-77, 223-225
 - Laboratory of Chemical Pharmacology, 77-79, 220-221
 - Laboratory of Chemistry, 79-80
 - Laboratory of Kidney and Electrolyte Metabolism, 80, 219
 - Laboratory of Molecular Cardiology, 81
 - Laboratory of Molecular Hematology, 81, 219
 - Laboratory of Technical Development, 81-82
- clinical research branches of, 69-72
 - Cardiology Branch, 69
 - Clinical Hematology Branch, 70
 - Hypertension-Endocrine Branch, 70, 221-222
 - Molecular Disease Branch, 71
 - Pathology Branch, 71
 - Pulmonary Branch, 71-72
 - Surgery Branch, 72
- formal instruction through FAES, 69
- interinstitute endocrinology training program, 8-9, 68-69
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 219-225
 - Hypertension-Endocrine Branch, 221-222
 - Laboratory of Biochemical Genetics, 222-223
 - Laboratory of Biochemistry, 219-220
 - Laboratory of Cell Biology, 222
 - Laboratory of Cellular Metabolism, 223-225
 - Laboratory of Chemical Pharmacology, 220-221
 - Laboratory of Kidney and Electrolyte Metabolism, 219
 - Laboratory of Molecular Hematology, 219
- medical staff fellows in pharmacology (PRAT), 68
- staff appointments in, 68

National Institute on Aging (NIA)

- Gerontology Research Center, 83
- medical staff fellows in, 83-84
- medical staff fellows in pharmacology (PRAT), 85, 179-180
- research branches and laboratories of, 85-93

- Laboratory of Behavioral Sciences, 86-87
- Laboratory of Biological Chemistry, 89-90
- Laboratory of Cardiovascular Sciences, 88-89
- Laboratory of Cellular and Molecular Biology, 90-91
- Laboratory of Clinical Physiology, 85
- Laboratory of Molecular Genetics, 89
- Laboratory of Neurosciences, 91-93, 179-180
- Laboratory of Personality and Cognition, 87-88
- Longitudinal Studies Branch, 85

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- appointments in clinical research, 94
- appointments in laboratory research, 94-95
 - Laboratory of Clinical Studies, 94, 96, 180-181
 - Laboratory of Metabolism and Molecular Biology, 94, 96-97
 - Laboratory of Physiologic and Pharmacologic Studies, 94, 97-98, 181-183
- laboratories participating in Pharmacology Research Associate Program of NICMS, 180-183
 - Laboratory of Clinical Studies, 180-181
 - Laboratory of Physiologic and Pharmacologic Studies, 181-183
- Unit for Special Projects, Office of the Scientific Director, 180
- medical staff fellows in pharmacology (PRAT), 95-96, 180-183
- Unit for Special Projects, Office of the Scientific Director, 95-96, 180

National Institute of Allergy and Infectious Diseases (NIAID)

- basic research laboratories of, 103-114
 - Biological Resources Branch, 110-111
 - Laboratory of Cellular and Molecular Immunology, 111-112
 - Laboratory of Immunogenetics, 105-106, 184
 - Laboratory of Immunology, 106-107
 - Laboratory of Immunopathology, 109-110
 - Laboratory of Infectious Diseases, 104-105
 - Laboratory of Microbial Structure and Function, 113
 - Laboratory of Molecular Microbiology, 108-109
 - Laboratory of Parasitic Diseases, 107-108
 - Laboratory of Pathobiology, 113-114
 - Laboratory of Persistent Viral Diseases, 112
 - Laboratory of Viral Diseases, 103-104, 184-185
- Rocky Mountain Laboratories, 112-114

- clinical branches of, 99-103
 - Laboratory of Clinical Investigation, 99, 100-101, 183
 - Laboratory of Immunoregulation, 99-100, 101-103, 184
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 183-185
 - Laboratory of Clinical Investigation, 183
 - Laboratory of Immunogenetics, 184
 - Laboratory of Immunoregulation—AIDS Clinical Study Section, 184
 - Laboratory of Viral Diseases, 184-185
- medical staff fellow appointments in, 99
- medical staff fellows in pharmacology (PRAT), 99

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- appointments in clinical research, 166
- clinical research branches of, 166-168
 - Arthritis and Rheumatism Branch, 166-167, 185
 - Laboratory of Physical Biology, 168, 185
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 185
 - Arthritis and Rheumatism Branch, 185
 - Laboratory of Physical Biology, 185
- medical staff fellows in pharmacology (PRAT), 166

National Institute of Child Health and Human Development (NICHD)

- appointments in clinical research, 134-135
- appointments in laboratory research, 135-136
- basic research laboratories of, 142-156
 - Cell Biology and Metabolism Branch, 154-156, 195
 - Endocrinology and Reproduction Research Branch, 152-154, 193-194
 - Laboratories of the Scientific Director, 142
 - Laboratory of Developmental and Molecular Immunity, 149-150
 - Laboratory of Developmental Neurobiology, 142-145, 196-197, 197-198
 - Laboratory of Developmental Pharmacology, 148-149, 196
 - Laboratory of Mammalian Genes and Development, 147-148
 - Laboratory of Molecular Genetics, 145-147
 - Laboratory of Theoretical and Physical Biology, 150-152, 197

- clinical research branches of, 136-142
 - Developmental Endocrinology Branch, 8, 136-138
 - Human Genetics Branch, 138-140
 - Laboratory of Comparative Ethology, 140-142
- formal instruction through FAES, 136
- Interinstitute Endocrinology Fellowship Program, 8, 134
- Interinstitute Medical Genetics Program, 10-11, 135
- Intramural Research Program, 133
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 193-198
 - Cell Biology and Metabolism Branch, 195
 - Endocrinology and Reproduction Research Branch, 193-194
 - Laboratory of Developmental Neurobiology, 196-197, 197-198
 - Laboratory of Developmental Pharmacology, 196
 - Laboratory of Theoretical and Physical Biology, 197
 - Office of the Scientific Director, 194
- medical staff fellows in pharmacology (PRAT), 136

National Institute on Deafness and Other Communication Disorders (NIDCD)

Speech and Voice Unit, 115

National Institute of Dental Research (NIDR)

- basic research laboratories of, 161-165
 - Bone Research Branch, 162
 - Clinical Investigations and Patient Care Branch, 160, 161-162
 - Laboratory of Cellular Development and Oncology, 161
 - Laboratory of Developmental Biology and Anomalies, 162-163, 198-199
 - Laboratory of Immunology, 163
 - Laboratory of Microbial Ecology, 163-164
 - Laboratory of Oral Medicine, 164, 199
 - Neurobiology and Anesthesiology Branch, 158-159, 164-165, 198
- clinical research branches of, 158-160
 - Clinical Investigations and Patient Care Branch, 160, 161-162
 - Diagnostic Systems Branch, 158
 - Epidemiology and Oral Disease Prevention Program, 159-160
 - Neurobiology and Anesthesiology Branch, 158-159, 164-165
- dental staff fellows in, 4, 157

- laboratories participating in Pharmacology Research Associate Program of NIGMS, 198-200
- Laboratory of Developmental Biology and Anomalies, 198-199
- Laboratory of Microbiology and Immunology, 199-200
- Laboratory of Oral Medicine, 199
- Neurobiology and Anesthesiology Branch, 198
- medical staff fellows in, 157-158
- medical staff fellows in pharmacology (PRAT), 158

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- appointments in clinical research, 116-117
- appointments in laboratory research, 117
- basic research laboratories of, 126-132
 - Laboratory of Biochemical Pharmacology, 126, 213-214
 - Laboratory of Biochemistry and Metabolism, 127, 204-205
 - Laboratory of Bioorganic Chemistry, 127-128, 202
 - Laboratory of Cell Biology and Genetics, 130, 206
 - Laboratory of Cellular and Developmental Biology, 131, 210-211
 - Laboratory of Chemical Biology, 123, 128, 209
 - Laboratory of Chemical Physics, 129, 203
 - Laboratory of Chemistry, 129-130
 - Laboratory of Molecular Biology, 130-131, 203
 - Mathematical Research Branch, 131-132
- developing programs, 117
- interinstitute endocrinology training program, 8
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 200-214
 - Clinical Endocrinology Branch, 206-207
 - Diabetes Branch, 207-209
 - Digestive Diseases Branch, 204
 - Genetics and Biochemistry Branch, 200
 - Laboratory of Analytical Chemistry, 209-210
 - Laboratory of Biochemical Pharmacology, 213-214
 - Laboratory of Biochemistry and Metabolism, 204-205
 - Laboratory of Bioorganic Chemistry, 202
 - Laboratory of Cell Biology and Genetics, 206
 - Laboratory of Cellular and Developmental Biology, 210-211
 - Laboratory of Chemical Biology, 209
 - Laboratory of Chemical Physics, 203

Laboratory of Molecular Biology, 203
 Laboratory of Molecular and Cellular Biology, 200-201
 Laboratory of Neuroscience, 211-212
 Laboratory of Structural Biology, 204
 Metabolic Diseases Branch, 205
 Molecular, Cellular and Nutritional Endocrinology Branch,
 201-202
 Molecular Pathophysiology Branch, 212-213
 medical staff fellows in epidemiology and clinical investigation,
 118-126
 Clinical Endocrinology Branch, 118-119, 206, 207
 Clinical Hematology Branch, 120
 Diabetes Branch, 121, 207-209
 Digestive Diseases Branch, 122, 204
 Genetics and Biochemistry Branch, 122-123, 200
 Laboratory of Chemical Biology, 123, 128, 209
 Metabolic Diseases Branch, 123-124, 205
 Molecular, Cellular and Nutritional Endocrinology Branch,
 119-120, 201-202
 Molecular Pathophysiology Branch, 124, 212-213
 Phoenix Clinical Research Section, 124-125
 Southwestern Field Studies Section, 125-126
 medical staff fellows in pharmacology (PRAT), 117

National Institute on Drug Abuse (NIDA)

laboratories participating in Pharmacology Research Associate
 Program of NIGMS, 214-215
 Laboratory of Molecular Pharmacology, 214
 Laboratory of Neuropharmacology, 214-215

National Institute of Environmental Health Sciences (NIEHS)

Division of Biometry and Risk Assessment, 173-175
 Computer Technology Branch, 175
 Epidemiology Branch, 175
 Laboratory of Biochemical Risk Analysis, 175
 Molecular Modeling Section, 174
 Statistics and Biomathematics Branch, 174-175
 Division of Intramural Research, 170-173
 Laboratory of Cellular and Molecular Pharmacology, 170-171
 Laboratory of Genetics, 173
 Laboratory of Molecular Biophysics, 172, 215-216

- Laboratory of Molecular Carcinogenesis, 173
- Laboratory of Molecular Genetics, 173
- Laboratory of Molecular and Integrative Neuroscience, 171-172
- Laboratory of Pulmonary Pathobiology, 172, 217-218
- Division of Toxicology Research and Testing, 176
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 215-219
 - Laboratory of Behavioral and Neurological Toxicology, 217
 - Laboratory of Molecular Biophysics, 215-216
 - Laboratory of Pharmacology, 218
 - Laboratory of Pulmonary Pathobiology, 217-218
 - Laboratory of Reproductive and Developmental Toxicology, 216-217
- Office of the Scientific Director, 219
- medical staff fellows in, 169-170
- medical staff fellows in pharmacology (PRAT), 170

National Institute of General Medical Sciences (NIGMS)

- clinical pharmacology program of, 178-179
- Pharmacology Research Associates in, 5, 16, 177
- pharmacology research fellowships in following participating NIH laboratories:
 - Arthritis and Rheumatism Branch (NIAMS), 185
 - Biological Psychiatry Branch (NIMH), 232-233
 - Cell Biology and Metabolism Branch (NICHD), 195
 - Clinical Center program, 5
 - Clinical Endocrinology Branch (NIDDK), 206-207
 - Clinical Neuroscience Branch (NIMH), 228-231
 - Clinical Pharmacology Branch (NCI), 190
 - Diabetes Branch (NIDDK), 207-209
 - Digestive Diseases Branch (NIDDK), 204
 - Endocrinology and Reproduction Research Branch (NICHD), 152-154, 193-194
 - Experimental Therapeutics Branch (NINDS), 235-236
 - Genetics and Biochemistry Branch (NIDDK), 200
 - Hypertension-Endocrine Branch (NHLBI), 221-222
 - Laboratory of Analytical Chemistry (NIDDK), 209-210
 - Laboratory of Behavioral and Neurological Toxicology (NIEHS), 217
 - Laboratory of Biochemical Genetics (NHLBI), 222-223
 - Laboratory of Biochemical Pharmacology (NCI), 189-190

Laboratory of Biochemical Pharmacology (NIDDK), 213-214
 Laboratory of Biochemistry (NHLBI), 219-220
 Laboratory of Biochemistry and Metabolism (NIDDK), 204-205
 Laboratory of Biological Chemistry (NCI), 187-188
 Laboratory of Bioorganic Chemistry (NIDDK), 202
 Laboratory of Cell Biology (NHLBI), 222
 Laboratory of Cell Biology (NIMH), 225-226
 Laboratory of Cell Biology and Genetics (NIDDK), 206
 Laboratory of Cellular Carcinogenesis and Tumor Promotion
 (NCI), 40-41, 186
 Laboratory of Cellular and Developmental Biology (NIDDK),
 210-211
 Laboratory of Cellular Metabolism (NHLBI), 223-225
 Laboratory of Cerebral Metabolism (NIMH), 226-227
 Laboratory of Chemical Biology (NIDDK), 209
 Laboratory of Chemical Pharmacology (NHLBI), 220-221
 Laboratory of Chemical Physics (NIDDK), 203
 Laboratory of Clinical Investigation (NIAID), 183
 Laboratory of Clinical Science (NIMH), 231-232
 Laboratory of Clinical Studies (NIAAA), 96, 180-181
 Laboratory of Developmental Biology and Anomalies (NIDR),
 198-199
 Laboratory of Developmental Neurobiology (NICHD), 196-197,
 197-198
 Laboratory of Developmental Pharmacology (NICHD), 196
 Laboratory of Experimental Carcinogenesis (NCI), 192
 Laboratory of Experimental Neuropathology (NINDS), 237-238
 Laboratory of Experimental Therapeutics and Metabolism
 (NCI), 186-187
 Laboratory of Human Carcinogenesis (NCI), 188
 Laboratory of Immunogenetics (NIAID), 184
 Laboratory of Immunoregulation (NIAID), 184
 Laboratory of Kidney and Electrolyte Metabolism (NHLBI), 219
 Laboratory of Mathematical Biology (NCI), 193
 Laboratory of Metabolism and Molecular Biology (NIAAA),
 96-97
 Laboratory of Microbiology and Immunology (NIDR), 199-200
 Laboratory of Molecular Biology (NCI), 190-191
 Laboratory of Molecular Biology (NIDDK), 203
 Laboratory of Molecular Biology (NIMH), 227-228
 Laboratory of Molecular Biophysics (NIEHS), 215-216

Laboratory of Molecular and Cellular Biology (NIDDK),
 200-201
 Laboratory of Molecular and Cellular Neurobiology (NINDS),
 236-237
 Laboratory of Molecular Hematology (NHLBI), 219
 Laboratory of Molecular Pharmacology (NIDA), 214
 Laboratory of Neurochemistry (NIMH), 227
 Laboratory of Neurochemistry (NINDS), 237
 Laboratory of Neuroparmacology (NIDA), 214-215
 Laboratory of Neurophysiology (NINDS), 234-235
 Laboratory of Neuroscience (NIDDK), 211-212
 Laboratory of Neurosciences (NIA), 179-180
 Laboratory of Oral Medicine (NIDR), 199
 Laboratory of Pharmacology (NIEHS), 218
 Laboratory of Physical Biology (NIAMS), 185
 Laboratory of Physiologic and Pharmacologic Studies (NIAAA),
 181-183
 Laboratory of Preclinical Pharmacology (NIMH), 234
 Laboratory of Pulmonary Pathobiology (NIEHS), 217-218
 Laboratory of Reproductive and Developmental Toxicology
 (NIEHS), 216-217
 Laboratory of Structural Biology (NIDDK), 204
 Laboratory of Theoretical and Physical Biology (NICHD), 197
 Laboratory of Tumor Virus Biology (NCI), 189
 Laboratory of Viral Diseases (NIAID), 184-185
 Metabolic Diseases Branch (NIDDK), 205
 Metabolism Branch (NCI), 191
 Molecular, Cellular and Nutritional Endocrinology Branch
 (NIDDK), 201-202
 Molecular Pathophysiology Branch (NIDDK), 212-213
 Neurobiology and Anesthesiology Branch (NIDR), 198
 Office of the Scientific Director (NICHD), 194
 Office of the Scientific Director (NIEHS), 219
 Unit for Special Projects, Office of the Scientific Director
 (NIAAA), 180
 program areas, 178

National Institute of Mental Health (NIMH)

appointments in clinical research, 239-240
 appointments in laboratory research, 240
 clinical and basic research branches of, 241-265

- Biological Psychiatry Branch, 232-233, 241-244
- Child Psychiatry Branch, 256
- Clinical Brain Disorders Branch, 264-265
- Clinical Neuroendocrinology Branch, 250-251
- Clinical Neurogenetics Branch, 256-258
- Clinical Neuroscience Branch, 228-231, 246-250
- Clinical Psychobiology Branch, 244-245
- Inpatient Research Unit, 245-246
- Laboratory of Cell Biology, 225-226, 258
- Laboratory of Cerebral Metabolism, 226-227, 259-260
- Laboratory of Clinical Science, 231-232, 252-256
- Laboratory of Developmental Psychology, 258
- Laboratory of General and Comparative Biochemistry, 259
- Laboratory of Molecular Biology, 227-228
- Laboratory of Neurochemistry, 227, 260
- Laboratory of Neurophysiology, 260-261
- Laboratory of Preclinical Pharmacology, 234, 265
- Laboratory of Psychology and Psychopathology, 258-259
- Neuropsychiatry Branch, 261-263
- Outpatient Research Unit, 246
- laboratories participating in Pharmacology Research Associate Program in NIGMS, 225-234
 - Biological Psychiatry Branch, 232-233
 - Clinical Neuroscience Branch, 228-231
 - Laboratory of Cell Biology, 225-226
 - Laboratory of Cerebral Metabolism, 226-227
 - Laboratory of Clinical Science, 231-232
 - Laboratory of Molecular Biology, 227-228
 - Laboratory of Neurochemistry, 227
 - Laboratory of Preclinical Pharmacology, 234
- medical staff fellows in pharmacology (PRAT), 241

National Institute of Neurological Disorders and Stroke (NINDS)

- appointments in clinical research, 266-267
- appointments in laboratory research, 267
- basic neurosciences laboratories, 275-285
 - Laboratory of Biophysics, 283
 - Laboratory of Central Nervous System Studies, 275-276
 - Laboratory of Experimental Neuropathology, 237-238, 280-281
 - Laboratory of Molecular Biology, 282-283

- Laboratory of Molecular and Cellular Neurobiology, 236-237, 283-285
- Laboratory of Neural Control, 278
- Laboratory of Neurobiology, 281
- Laboratory of Neurochemistry, 237, 278-279
- Laboratory of Neuronal Regeneration and Implantation, 279
- Laboratory of Neuropathology and Neuroanatomical Sciences, 280
- Laboratory of Neuropsychology, 234-235, 281-282
- Laboratory of Viral and Molecular Pathogenesis, 277-278
- clinical branches of, 268-275
 - Clinical Neuroscience Branch, 268
 - Developmental and Metabolic Neurology Branch, 269-270
 - Experimental Therapeutics Branch, 235-236, 270-271
 - Medical Neurology Branch, 271-272
 - Neuroepidemiology Branch, 272-273
 - Neuroimmunology Branch, 273
 - Office of the Clinical Director, 274-275
 - Surgical Neurology Branch, 273-274
- laboratories participating in Pharmacology Research Associate Program of NIGMS, 234-238
 - Experimental Therapeutics Branch, 235-236
 - Laboratory of Experimental Neuropathology, 237-238
 - Laboratory of Molecular and Cellular Neurobiology, 236-237
 - Laboratory of Neurochemistry, 237
 - Laboratory of Neurophysiology, 234-235
- medical staff fellows in pharmacology (PRAT), 267

National Naval Medical Center (NNMC)

- NCI-Navy Medical Oncology Branch, 52-53

Neoplasms

- see** Oncology

Nervous System

- see** Neurology

Neurology

- see also** National Institute of Mental Health (NIMH); National Institute of Neurological Disorders and Stroke (NINDS)
- credit towards board certification in, 7

Laboratory of Behavioral and Neurological Toxicology (NIEHS),
217
Laboratory of Developmental Neurobiology (NICHD), 142-145,
196-197, 197-198
Laboratory of Molecular and Integrative Neuroscience (NIEHS),
171-172
Laboratory of Neurosciences (NIA), 91-93, 179-180
Laboratory of Physiologic and Pharmacologic Studies (NIAAA),
94, 97-98, 181-183
Laboratory of Sensorimotor Research (NEI), 61-62
Neurobiology and Anesthesiology Branch (NIDR), 158-159,
164-165

Nuclear Medicine

approved residency training program in, 6, 292
Nuclear Medicine Department (CC), 2, 292

Nutrition

see Metabolism and Nutrition

Obstetrics

see Gynecology and Obstetrics

Oncology

see also National Cancer Institute (NCI)
Laboratory of Cellular Development and Oncology (NIDR), 161
Laboratory of Molecular Carcinogenesis (NIEHS), 173
medical oncology, credit towards board certification in, 7
Molecular Modeling Section (NIEHS), 174
pediatric oncology, credit towards board certification in, 8
Statistics and Biomathematics Branch (NIEHS), 174-175

Ophthalmology

see National Eye Institute (NEI)

Oral Medicine

see National Institute of Dental Research (NIDR)

Parasitic Diseases

see Microbiology

Pathology

anatomical pathology, approved residency training program in, 6
Clinical Pathology Department (CC), 3, 286-290
clinical pathology, fellowships in, 3
Laboratory of Experimental Neuropathology (NINDS), 237-238, 280-281
Laboratory of Experimental Pathology (NCI), 41
Laboratory of Immunopathology (NIAID), 109-110
Laboratory of Neuropathology and Neuroanatomical Sciences (NINDS), 280
Laboratory of Ophthalmic Pathology (NEI), 63
Laboratory of Pathobiology (NIAID), 113-114
Laboratory of Pathology (NCI), 28-29
Laboratory of Pulmonary Pathobiology (NIEHS), 172
Pathology Branch (NHLBI), 71

Pediatrics

see also National Institute of Child Health and Human Development (NICHD)
Child Psychiatry Branch (NIMH), 256
credit towards board certification in, 7-8
 pediatric endocrinology, 7
 pediatric genetics, 7
 pediatric hematology/oncology, 8
Pediatric Oncology Branch (NCI), 53-54

Pharmacology

see also Toxicology
Clinical Pharmacology Branch (NCI), 190
clinical pharmacology program of NIGMS, 178-179
Clinical Psychobiology Branch (NIMH), 244-245
Developmental and Metabolic Neurology Branch (NINDS), 269-270
Developmental Therapeutics Program (NCI), 56-58
 Laboratory of Biochemical Pharmacology, 57, 189-190
 Laboratory of Biological Chemistry, 56-57, 187-188
 Laboratory of Molecular Pharmacology, 57-58
 medical staff fellows in, 56-58
Experimental Therapeutics Branch (NINDS), 235-236, 270-271
Laboratory of Biochemical Pharmacology (NIDDK), 126, 213-214
Laboratory of Bioorganic Chemistry (NIDDK), 127-128, 202

Laboratory of Cellular and Molecular Pharmacology (NIEHS),
 170-171
 Laboratory of Chemical Pharmacology (NHLBI), 77-79, 220-221
 Laboratory of Clinical Science (NIMH), 231-232, 252-256
 Laboratory of Developmental Neurobiology (NICHD), 142-145,
 196-197, 197-198
 Laboratory of Developmental Pharmacology (NICHD), 148-149,
 196
 Laboratory of Molecular Pharmacology (NIDA), 214
 Laboratory of Neuropharmacology (NIDA), 214-215
 Laboratory of Neurophysiology (NINDS), 234-235, 281-282
 Laboratory of Pharmacology (NIEHS), 218
 Laboratory of Physiologic and Pharmacologic Studies (NIAAA),
 94, 97-98, 181-183
 Laboratory of Preclinical Pharmacology (NIMH), 234, 265
 Laboratory of Theoretical and Physical Biology (NICHD),
 150-152, 197
 Medicine Branch (NCI), 51-52
 Pediatric Oncology Branch (NCI), 53-54

Pharmacology Research Fellowships

see under National Institute of General Medical Sciences
 (NIGMS)

Physics

see also Biophysics

Laboratory of Chemical Physics (NIDDK), 129, 203
 Laboratory of Physical Biology (NIAMS), 168, 185
 Laboratory of Theoretical and Physical Biology (NICHD),
 150-152, 197

Physiology

Bone Research Branch (NIDR), 162
 Laboratory of Clinical Physiology (NIA), 85-86
 Laboratory of Developmental Neurobiology (NICHD), 142-145,
 196-197, 197-198
 Laboratory of Neural Control (NINDS), 278
 Laboratory of Neurophysiology (NIMH), 260-261
 Laboratory of Neurophysiology (NINDS), 234-235, 281-282
 Laboratory of Neurosciences (NIA), 91-93, 179-180

Laboratory of Physiologic and Pharmacologic Studies (NIAAA),
94, 97-98, 181-183

Laboratory of Pulmonary Pathobiology (NIEHS), 217-218

Laboratory of Sensorimotor Research (NEI), 61-62

Molecular Pathophysiology Branch (NIDDK), 212-213

Psychiatry

see also National Institute of Mental Health (NIMH)

credit towards board certification in, 8

Psychology

see also Behavior

Biological Psychiatry Branch (NIMH), 232-233, 241-244

Child Psychiatry Branch (NIMH), 256

Clinical Neuroscience Branch (NIMH), 228-231, 246-250

Laboratory of Comparative Ethology (NICHD), 140-142

Laboratory of Personality and Cognition (NIA), 87-88

Public Health Service

requirements for appointment as medical staff fellow, 12

Radiology and Radiotherapy

Radiation Epidemiology Branch (NCI), 48

Radiation Oncology Branch (NCI), 54-55

Reproduction

Developmental Endocrinology Branch (NICHD), 8, 136-138

Endocrinology and Reproduction Research Branch (NICHD),
152-154, 193-194

Laboratory of Reproductive and Developmental Toxicology
(NIEHS), 216-217

reproductive endocrinology, credit towards board certification in, 8

Statistics and Biomathematics Branch (NIEHS), 174-175

Residency Programs

approved training Nuclear Medicine Department (CC), 292

approved training programs, 6-8

Respiratory System

Laboratory of Pulmonary Pathobiology (NIEHS), 172, 217-218

Laboratory of Technical Development (NHLBI), 81-82

Pulmonary Branch (NHLBI), 71-72

Rheumatology

Arthritis and Rheumatism Branch (NIAMS), 166-167, 185

credit towards board certification in, 8

Seminars and Lectures

combined clinical staff conferences and lectures available to fellows, 296-299

Skin Diseases

see National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Staff Fellowships

see Medical Staff Fellowships

Staff Physicians

appointments as, 5

Statistics

see also Biometry

Biostatistics Branch (NCI), 48

Epidemiology and Biostatistics Program (NCI), 47

Laboratory of Theoretical and Physical Biology (NICHHD),
150-152, 197

Statistics and Biomathematics Branch (NIEHS), 174-175

Stroke

see National Institute of Neurological Disorders and Stroke (NINDS)

Surgery

medical staff fellows in surgery in NHLBI, 67-68

Surgery Branch (NCI), 55

Surgery Branch (NHLBI), 67, 72

Surgical Neurology Branch (NINDS), 273-274

Technology

see Instrumentation and Methodology

Toxicology

see also Mutagenesis

Division of Toxicology Research and Testing (NIEHS), 176

Laboratory of Behavioral and Neurological Toxicology (NIEHS),
217

Laboratory of Developmental Pharmacology (NICHD), 148-149,
196

Laboratory of Pulmonary Pathobiology (NIEHS), 217-218

Laboratory of Reproductive and Developmental Toxicology
(NIEHS), 216-217

Transfusion Medicine

approved residency training programs in, 7

credit towards board certification in, 8

Department of Transfusion Medicine (CC), 2, 3, 286

fellowships in, 3, 286

Urogenital System

Laboratory of Kidney and Electrolyte Metabolism (NHLBI), 80,
219

nephrology, developing programs in NIDDK, 117

Viruses and Viral Diseases

see Microbiology

Vision

see National Eye Institute (NEI)

Voice

see National Institute on Deafness and Other Communication
Disorders (NIDCD)

Warren Grant Magnuson Clinical Center (CC)

approved training programs, 6-8

Bioethics Program, 292-293

clinical electives for medical students, 5-6

Clinical Pathology Department, 3, 286-290

- Clinical Chemistry Service, 287
- Hematology Service, 288
- Immunology Service, 288-289
- Laboratory Computer Service, 290
- Microbiology Service, 289-290
- Critical Care Medicine Department, 3, 290-292
- Department of Transfusion Medicine, 2, 3, 286
- Endocrinology Fellowship Program, 8-9
 - internal medicine and endocrinology board examinations, 9
 - lectures and courses, 9
 - medical student program, 9
- general description of, 1-3
- Interinstitute Medical Genetics Program, 10-11, 135
- Medical Information System, 2
- Medical Staff Fellowship Program, 3-4
 - dental staff fellows, 4, 157
 - medical staff fellow in pharmacology sponsored by NIGMS, 5
- Nuclear Medicine Department, 2, 3, 292
- staff physicians, 5

Library Building 10
National Institutes of Health
Bethesda, MD 20892



<http://nihlibrary.nih.gov>

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

Use of funds for printing this periodical has been approved by the
Director of the Office of Management and Budget through
September 30, 1989.

NIH LIBRARY



3 1496 00427 1121